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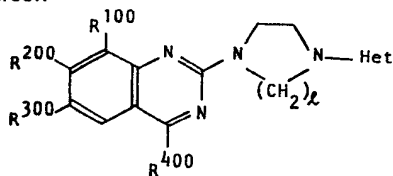
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(54) Quinazoline derivatives and antihypertensive preparations containing same as effective components.

(57) Disclosed herein is an antihypertensive preparation containing, as an active component, a novel quinazoline derivative represented by the following general formula or a salt thereof:



wherein R¹⁰⁰ means a hydrogen atom or methoxy group, R²⁰⁰ and R³⁰⁰ denote individually a hydrogen atom or lower alkoxy group, R⁴⁰⁰ is a hydrogen atom or amino group, *l* stands for 2 or 3, and Het is a specific hetero ring group.

SPECIFICATIONTitle of the Invention:

Quinazoline Derivatives and Antihypertensive
Preparations Containing Same as Effective
Components

5 Background of the Invention:

1) Field of the Invention:

This invention relates to novel quinazoline
derivatives useful for the treatment of hypertension.

2) Description of the Prior Art:

10 Numerous quinazoline derivatives have been known
to date, including especially piperazinoquinazolines
such as various acid amide compounds, e.g., prazosin
(Japanese Patent Publication No. 22135/1970; U.S.
Patent No. 3,511,836), terazosin (Japanese Patent Laid-
15 Open No. 27588/1979; U.S. Patent Nos. 4,026,894 and
4,112,097) and those disclosed in Japanese Patent Laid-
Open No. 116052/1982 as well as piperazinoquinazoline
of the pyrimidine structure such as those disclosed in
Japanese Patent Laid-Open No. 181068/1982. These
20 conventional quinazoline derivatives have been
subjected to further investigations, whereby some of
the quinazoline derivatives have already been

clinically applied as antihypertensive agents. They are classified as α -adrenergic antihypertensive agents. Although they have excellent clinical effects, some drawbacks have been observed that they lack long-acting properties and develop orthostatic hypotension as an undesirable side effect.

Summary of the Invention:

An object of this invention is to provide novel quinazoline derivatives and their salts.

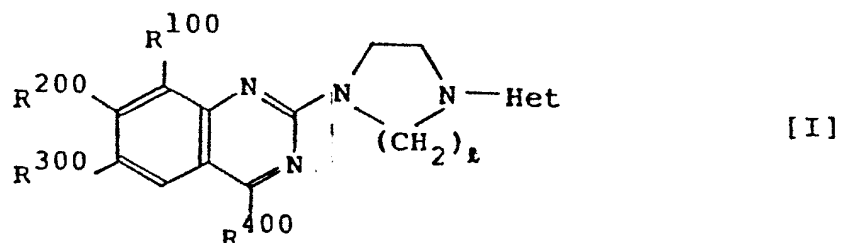
10 Another object of this invention is to provide antihypertensive preparations which contain these compounds as active components.

A further object of this invention is to provide a process for the preparation of these compounds.

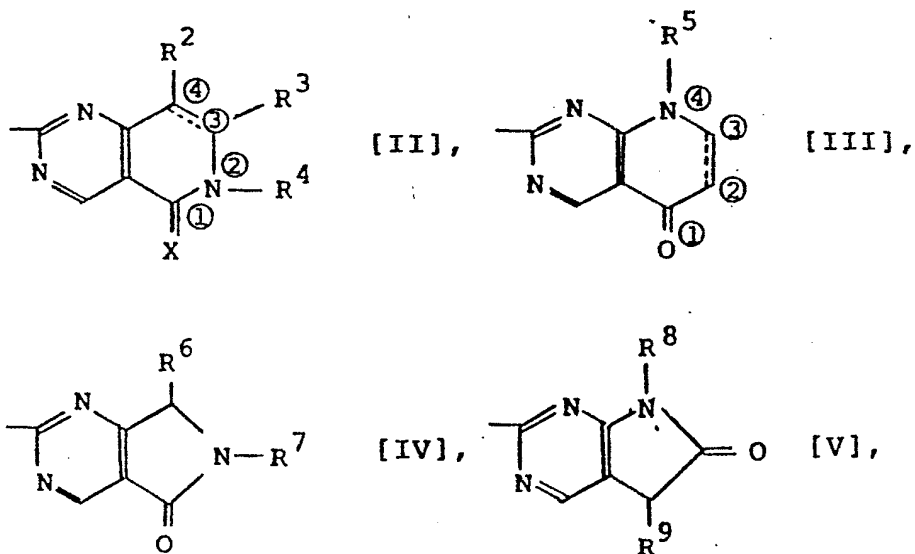
15 The present inventors have found through zoopery that compounds represented by the below-described general formula [I] have extremely strong and long-acting antihypertensive effects and can reduce or substantially avoid the development of the above-mentioned orthostatic hypotension compared with the
20 conventional compounds, leading to completion of this invention.

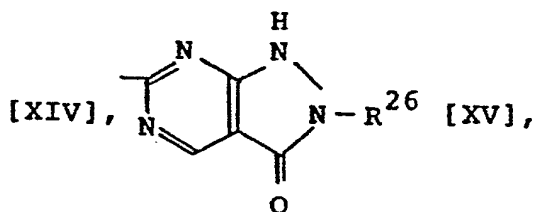
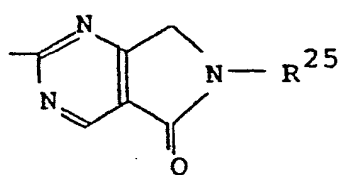
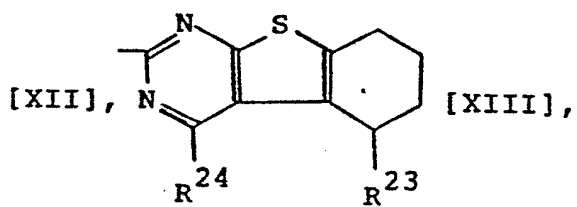
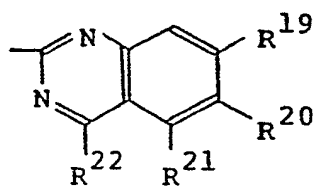
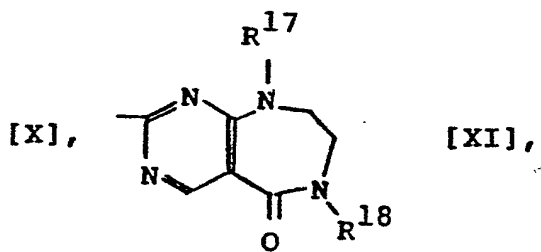
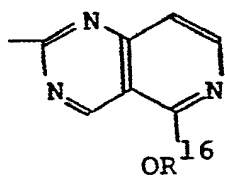
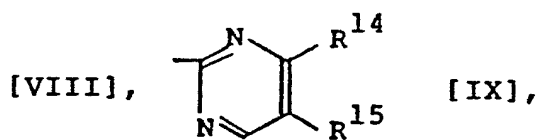
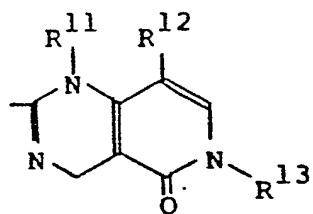
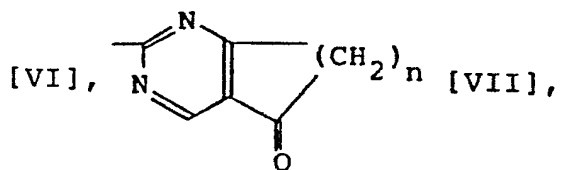
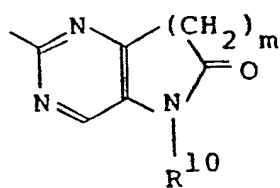
This invention provides, as an invention on materials, a quinazoline derivative represented by the

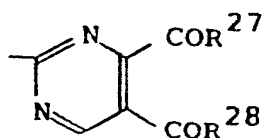
following general formula [I] or a pharmacologically acceptable salt thereof:



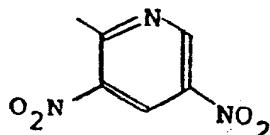
wherein R¹⁰⁰ means a hydrogen atom or methoxy group, R²⁰⁰ and R³⁰⁰ denote individually a hydrogen atom or lower alkoxy group, R⁴⁰⁰ is a hydrogen atom or amino group, *l* stands for 2 or 3, and Het is represented by any one of the following formulae [II] through [XIX]:



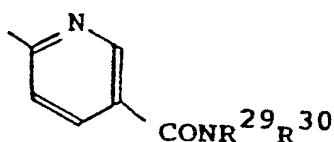




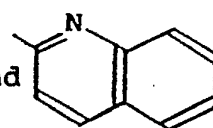
[XVI],



[XVII],



[XVIII], and



[XIX]

wherein,

in the formula [II], either single or double bond is formed between the 3- and 4-positions, R^2 means a hydrogen atom or a lower alkyl, aralkyl, cyano or formyl group, R^3 denotes a hydrogen atom or a lower alkoxy-carbonyl or phenyl group, R^4 is a hydrogen atom or a lower alkyl, lower cycloalkyl, hydroxy-substituted lower alkyl, lower alkoxy-substituted lower alkyl, phenyl or aralkyl group, and X stands for an oxygen or sulfur atom,

in the formula [III], either single or double bond is formed between the 2- and 3-positions, and R^5 means a hydrogen atom or a lower alkyl group,

in the formula [IV], R^6 and R^7 mean individually a hydrogen atom or a lower alkyl group,

in the formula [V], R^8 and R^9 mean
individually a hydrogen atom or a lower alkyl group,

in the formula [VI], m stands for 2 or 3, and
 R^{10} means a hydrogen atom or a lower alkyl group,

5 in the formula [VII], n stands for an integer of
from 2 to 4,

in the formula [VIII], R^{11} to R^{13} mean
individually a hydrogen atom or a lower alkyl group,

in the formula [IX], R^{14} means a hydrogen atom
10 or a hydroxyl, lower alkyl, $-NR^{31}R^{32}$ in which R^{31}
is a hydrogen atom or a lower alkyl group and R^{32} is
a hydrogen atom or a lower alkyl or lower acyl group,
lower alkylthio or lower alkoxy group, R^{15} denotes a
lower acyl, lower alkoxycarbonyl, $-CONR^{33}R^{34}$ in
15 which R^{33} is a hydrogen atom or a lower alkyl group,
 R^{34} is a hydrogen atom or a lower alkyl, phenyl,
aralkyl, halogen-substituted lower alkyl or cycloalkyl
group or R^{33} and R^{34} couples together to form a
methylene moiety which in turn forms a ring having 4 to
20 5 carbon atoms together with the associated nitrogen
atom, $-CONHNR^{35}R^{36}$ in which R^{35} and R^{36} are
individually a lower alkyl group, $-CH_2CONHR^{37}$ in
which R^{37} is a lower alkyl, or cyano group,
in the formula [X], R^{16} means a lower alkyl
25 group,

in the formula [XI], R^{17} and R^{18} mean individually a hydrogen atom or a lower alkyl group,

in the formula [XII], R^{19} through R^{21} means a hydrogen atom or a lower alkoxy group, and R^{22} denotes $-NR^{38}R^{39}$ in which R^{38} and R^{39} are individually a hydrogen atom or a lower alkyl group, or a hydrogen atom,

in the formula [XIII], R^{23} means a hydrogen atom or a lower alkyl group, and R^{24} denotes a hydrogen atom or a lower alkylthio group,

in the formula [XIV], R^{25} means an alkyl, cycloalkyl, hydroxy-substituted lower alkyl group, lower alkoxy-substituted lower alkyl, di(lower alkylamino)-substituted lower alkyl or aralkyl group,

in the formula [XV], R^{26} means a lower alkyl group,

in the formula [XVI], R^{27} and R^{28} are either same or different and mean individually a lower alkoxy, hydroxyl or lower alkylamino group, or R^{27} and R^{28} couples together to form a lower alkyl-substituted imino group, and

in the formula [XVIII], R^{29} and R^{30} are either same or different and mean individually a lower alkyl group; and as an invention on utility, an antihypertensive preparation containing the quinazoline

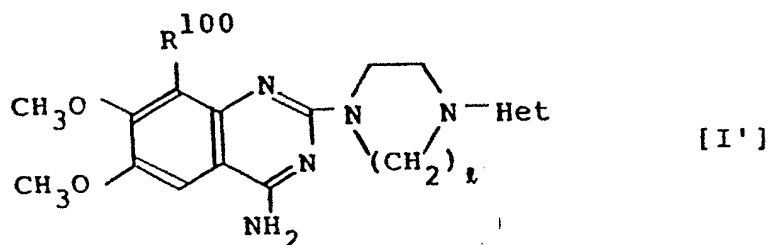
derivative or its pharmacologically acceptable salt as an active component.

Particularly preferred compounds include those having the general formula [I] in which R^{200} and R^{300} are individually a methoxy group, R^{400} denotes an amino group and Het is represented by any one of the formulae [III] through [XIII]; those having the general formula [I] in which R^{100} denotes a hydrogen atom, R^{200} and R^{300} denote individually a methoxy group, R^{400} is an amino group, l stands for 2 and Het is represented by any one of the formulae [XIV] through [XIX]; and those having the general formula [I] in which R^{100} and R^{400} mean individually a hydrogen atom, l stands for 2 and Het is represented by the formula [II] wherein a double bond is formed between the 3- and 4-positions, R^2 and R^3 mean individually a hydrogen atom, X denotes an oxygen atom and R^4 is a lower alkyl group.

Detailed Description of the Preferred Embodiments:

[Materials of the Invention]

Although materials of the present invention are the compounds represented by the general formula [I], the compounds represented by the following formula [I'] will next be mentioned as one of preferred embodiments of this invention:



wherein R^{100} means a hydrogen atom or methoxy group, the former being preferred, and 1 stands for 2 or 3 with 2 being preferred.

In the above formula [I'], Het is represented by
 5 any one of the formulae [II] to [XIII].

In the formula [II], as the lower alkyl group represented by R^2 , may be mentioned by way of example methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group or the like with methyl group being preferred. As an exemplary aralkyl group, may be mentioned benzyl group, diphenyl methyl group or the like with benzyl group being preferred. R^3 is a hydrogen atom or a lower alkoxy carbonyl or phenyl group
 15 with a hydrogen atom being preferred. Illustrative of the lower alkoxy carbonyl group may be methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group and the like. Among these groups, ethoxycarbonyl group is preferred. As the lower alkyl group represented by
 20 R^4 , the lower alkyl group represented above by R^2 may be mentioned. The lower cycloalkyl group contains

3 - 5 carbon atoms with a cyclopropyl group being preferred. As an exemplary hydroxy-substituted lower alkyl group, may be mentioned a methylol group, ethylol group or the like with an ethylol group being preferred. Illustrative of the lower alkoxy-substituted lower alkyl group may be a methoxymethyl group, ethoxymethyl group, methoxyethyl group, ethoxyethyl group and so on. Of these, a methoxyethyl group is preferred. As the aralkyl group, may be mentioned that represented above by R^2 .

In the formula [IIII], as the lower alkyl group represented by R^5 , may be mentioned the lower alkyl group represented above by R^2 with an ethyl group being preferred.

In the formula [IV], as the lower alkyl group represented by each of R^6 and R^7 , may be mentioned the lower alkyl group represented above by R^2 . A hydrogen atom is preferred as R^6 .

As the lower alkyl groups represented respectively by R^8 through R^{14} in the formulae [V], [VI], [VIIII] and [IX], may be mentioned those represented above by R^2 . In the formula [V], a lower alkyl group is preferred as R^8 while a hydrogen atom is preferred as R^9 . In the formula [VI], m is preferably 3 and R^{10} denotes preferably a lower alkyl group. In the formula [VII], n stands preferably for

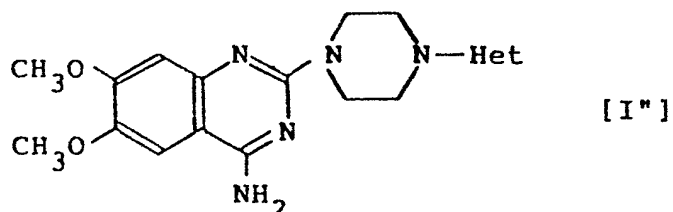
3. In the formula [VIII], R^{11} and R^{12} mean individually and preferably a hydrogen atom and R^{13} is preferably a lower alkyl group.

In $-NR^{31}R^{32}$ as R^{14} in the formula [IX], as
5 exemplary lower alkyl groups represented respectively by R^{31}, R^{32} , may be mentioned those represented above by R^2 . Illustrative of the lower acyl group represented by R^{32} may be an acetyl group, propionyl group, butyryl group and the like. Of these, an acetyl
10 group is preferred. As exemplary lower alkylthio groups represented by R^{14} , may be mentioned a methylthio group, ethylthio group and the like with the former group being preferred. As the lower alkoxy group, may for example be mentioned a methoxy group,
15 ethoxy group, propoxy group, isopropoxy group, butoxy group or the like with a methoxy group being preferred. As the lower acyl group represented by R^{15} , may be mentioned that represented above by R^{32} with an acetyl group being preferred. Illustrative of the
20 lower alkoxy carbonyl group may be a methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group and the like. As the lower alkyl groups represented respectively by R^{33} and R^{34} , may be mentioned those
25 represented above by R^2 . R^{33} and R^{34} may be either same or different. Illustrative of the aralkyl

represented by R^{34} may be those represented above by R^2 . A benzyl group is preferred as the aralkyl group. As exemplary halogen-substituted lower alkyl groups, may be mentioned a trifluoromethyl group, 2-fluoroethyl group, 2,2,2-trifluoroethyl group, 2,2,3,3,3-pentafluoropropyl group, 2-chloroethyl group, and so on. Of these, a 2,2,2-trifluoroethyl group is preferred. As the cycloalkyl group, may for example be mentioned a cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or the like with a cyclohexyl group being preferred. As the lower alkyl groups represented respectively by R^{35} to R^{37} in $-\text{CONHNR}^{35}\text{R}^{36}$ and $-\text{CH}_2\text{CONHR}^{37}$, may be mentioned those represented above by R^2 .

In the formulae [X] through [XIII], illustrative of the lower alkyl groups represented respectively by R^{16} to R^{21} , R^{23} , R^{38} and R^{39} may be those represented above by R^2 . As the alkylthio group represented by R^{24} , may be mentioned that represented above by R^{14} . In the formula [XI], each of R^{17} and R^{18} is preferably a lower alkyl group. As R^{23} in the formula [XIII], a lower alkyl group is preferred. As R^{24} , a lower alkylthio group is preferred.

Furthermore, the compounds represented by the following formula [I"] may also be mentioned as another preferred embodiment of this invention.



In the above formula [I*], Het is represented by the formula [XIV] or [XIX].

In the formula [XIV], the alkyl group represented by R^{25} contains 5 or more carbon atoms.

- 5 As such alkyl groups, may for example be mentioned amyl groups such as n-amyl group, hexyl groups such as n-hexyl groups, heptyl groups such as n-heptyl group, octyl groups such as n-octyl groups, etc. Among these alkyl groups, n-heptyl group is particularly preferred.
- 10 As exemplary cycloalkyl groups represented by R^{25} , may be mentioned those containing 4 to 7 carbon atoms with cyclohexyl group containing 6 carbon atoms being particularly preferred. As illustrative hydroxy-substituted lower alkyl groups represented by R^{25} ,
- 15 may be mentioned methylol group and ethylol groups. Of these, the latter group is preferred. As exemplary lower alkoxy-substituted lower alkyl groups represented by R^{25} , may be mentioned those containing 2 - 8 carbon atoms, for example, methoxymethyl group,
- 20 ethoxy-methyl group, methoxyethyl group, ethoxyethyl group and so on. Of these, methoxyethyl group is

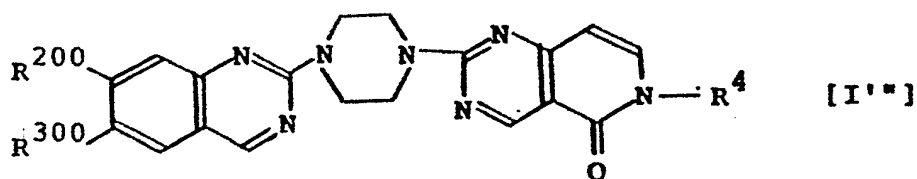
preferred. As the lower(alkyl)amino-substituted lower alkyl group represented by R^{25} , may for example be mentioned 2-dimethylaminoethyl group, 2-diethylaminoethyl group or the like. Of these, the former is preferred. As illustrative aralkyl groups represented by R^{25} , may be mentioned benzyl group, diphenylmethyl group, triphenyl methyl group, 2-phenylethyl group and so on. Of these, benzyl group and 2-phenylethyl group are preferred. In the formula [XV], illustrative of the lower alkyl group represented by R^{26} may be methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group and tert-butyl group with methyl group being preferred.

In the formula [XVI], as exemplary lower alkoxy groups represented by R^{27} or R^{28} , may be mentioned methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, etc. Among these groups, ethoxy groups is especially preferred. In addition, illustrative of the lower(alkyl)amino group represented by R^{27} or R^{28} may be methylamino group, ethylamino group, n-propylamino group, isopropylamino group, n-butylamino group, isobutylamino group, sec-butylamino group, tert-butylamino group and so on. Among these groups, ethylamino group is particularly preferred. As the lower alkyl group in the lower(alkyl)-substituted imino group represented by R^{27} or R^{28} , any one of

the lower alkyl groups referred to above by way of example for R^{26} may be mentioned with ethyl group being preferred.

In the formula [XVIII], the lower alkyl groups mentioned above for R^{26} may be mentioned as exemplary lower alkyl groups represented by R^{29} and R^{30} .

As a further preferred embodiment of this invention, may be mentioned the compounds represented by the following formula [I']:



In the above formula [I'], R^{200} and R^{300} individually means a hydrogen atom or lower alkoxy group and R^4 denotes a lower alkyl group. As exemplary lower alkoxy groups represented by R^{200} or R^{300} , may be mentioned methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group and the like with methoxy group being preferred. Where R^{200} stands for a hydrogen atom, it is preferred that R^{300} stands also for a hydrogen atom. Similarly, where R^{200} stands for a lower alkoxy group, it is preferred that R^{300} is also a lower alkoxy group. In the latter case, R^{200} and R^{300} may be different from

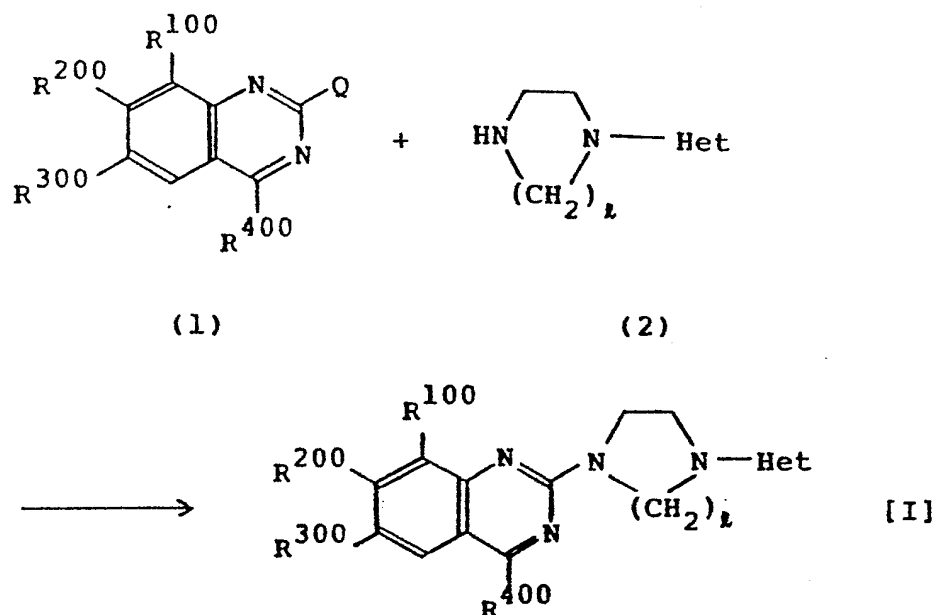
each other. Furthermore, as exemplary lower alkyl groups represented by R⁴, methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group and tert-butyl group may be
5 mentioned by way of example. Among these groups, ethyl group is preferred.

Certain specific exemplary compounds of this invention will be described in Examples, which will be given later in this specification. As pharmacolo-
10 gically acceptable salts of the compound [I] of this invention, may be mentioned, by way of example, those obtained in combination with acids capable of forming pharmacologically-acceptable nontoxic acid addition salts which may optionally contain anions, such as its
15 hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, acid phosphate, acetate, maleate, fumarate, succinate, lactate, tartrate, benzoate, citrate, gluconate, saccharate, methanesulfonate and p-toluenesulfonate. Hydrates of such salts are also
20 embraced in the compounds of this invention.

[Preparation process]

The compounds of this invention may be prepared in a process known per se in the art, for example, in accordance with the process described in Japanese
25 Patent Laid-Open No. 181068/1982. Namely, an exemplary

preparation process may be indicated by the following equation.



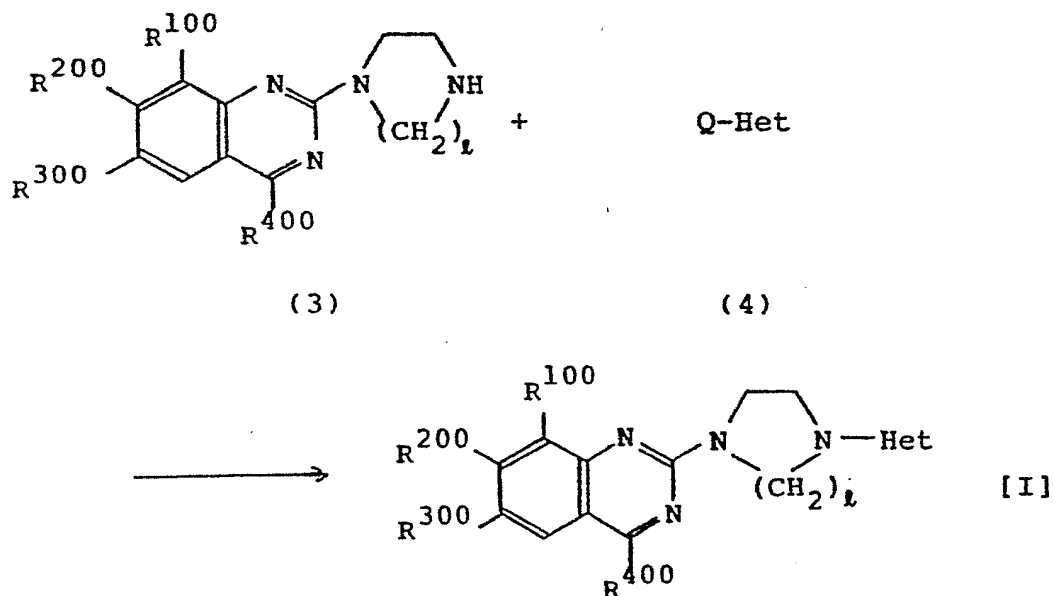
wherein Q means a readily-removable group such as a halogen atom, C₁₋₄ alkoxy group or C₁₋₄ alkylthio group with Cl being preferred.

The compound (1) employed in the above reaction is a known material, while as the compound (2), any one of compounds synthesized respectively in the below-given Referential Examples may be used. Compounds which will not be found in the Referential Examples but fall within the definition for the compound (2) may also be synthesized following the Referential Examples and may also be used.

The reaction may be carried out by reacting the compounds (1) and (2), for example, in a suitable

solvent such as isoamyl alcohol or n-butanol, under reflux, for example, at 100 to 150°C and for about 1 to 6 hours. The temperature and time and type of the solvent may be changed suitably in accordance with the types of the compounds (1) and (2). In the above reaction, the compound [I] can usually be obtained as a free base by adding a tertiary amine such as triethylamine or the like to the reaction system. Alternatively, the above reaction can directly provide the hydrochloride of the compound [I] unless such a tertiary amine is employed.

The compound [I] may also be synthetically prepared by the following reaction:



wherein Q is as defined above.

The thus-prepared compound [I] may be isolated and purified by a usual method. Furthermore, its acid addition salts led by its hydrochloride may also be obtained by a usual method, for example, by reacting
5 the compound [I] with an acid in an inert organic solvent, isolating the resulting precipitate, and if necessary purifying same.

[Invention on Drug]

As already described above, the compound [I] of
10 this invention has a strong antihypertensive effect. It is also expected to show some effects for the improvement of heart failure. The compound of the formula [I] is generally used in the form of pharmaceutical preparations and administered through
15 various routes such as oral, subcutaneous, intramuscular, intravenous, endonasal, skin-penetrative and rectal routes.

The present invention includes pharmaceutical preparations each of which is composed of a
20 pharmaceutically-acceptable carrier and as an active component, the compound of the general formula [I] or its acid addition salt. When producing preparations of this invention, they may be formed into tablets, capsules, powders, granules, troches, sansi (synchyses), cachets, elixirs, emulsions, solutions, syrups,
25 suspensions, aerosols, ointments, formed poultices,

tapes, soft and hard gelatin capsules, suppositories, sterile parenteral solutions, packed sterile powders, etc. Examples of the pharmaceutically-acceptable carrier include lactose, glucose, sucrose, sorbitol, mannitol, corn starch, crystalline cellulose, gum arabic, calcium phosphate, alginate, calcium silicate, microcrystalline cellulose, polyvinyl pyrrolidone, tragacanth gum, gelatin, syrup, methylcellulose, carboxymethylcellulose, methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate, inert polymers, water, mineral oil, etc.

Both solid and liquid preparations may contain one or more of the above-mentioned fillers, binders, lubricants, wetting agents, disintegrators, emulsifying and suspending agents, preservatives, sweetening agents and/or aromatics. The preparations may each be formulated in such a way that after administration to patients, its active component is released in a rapid, long-acting or sustained fashion.

For oral administration, the compound of the formula [I] is mixed with a carrier and diluent and is then formed into tablets, capsules or the like. For parenteral administration, the active component is dissolved in a 10% aqueous solution of glucose, isotonic saline, sterilized water or an analogous liquid and is then sealed in vials or ampuls for its

administration into veins by drip infusion or injection or its intramuscular injection. Advantageously, a solubilizer, local anesthetic, preservative and/or buffer may also be incorporated in the medium. It is
5 also feasible to lyophilize the preparation after its sealing in vials or ampuls. As other preparation forms for parenteral administration, may be mentioned those administrable percutaneously, such as ointments and cataplasms. For such parenteral administration, formed
10 poultices and tapes are advantageous.

The preparation of this invention may contain an active component in an amount of 0.005 - 200 mg, more generally, 0.02 - 50 mg per unit dosage.

The compound of the general formula [I] is
15 effective over a wide range of dosage. For example, its dosage per day may generally range from 0.0001 mg/Kg to 200 mg/Kg. The amount of the compound to be administered actually varies depending on the type of the compound and may be determined by physician
20 depending on the age, weight and sensitivity of each patient, the seriousness in symptom of the patient, the administration route, etc. Therefore, the above dosage range shall not be interpreted as limiting the scope of this invention. The preparation of this invention may
25 be administered 1 - 6 times a day with 1 - 4 times being usually suitable.

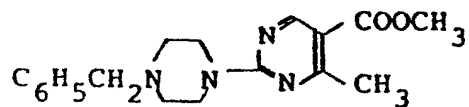
Although the compound of the formula [I] is by itself an effective antihypertensive agent, it may be administered, if necessary, in combination with one or more other antihypertensive agents and/or diuretics.

5 Such additional drugs may include methyldopa, hydralazine, nifedipine, nicardipine, amyloride, propranolol, pindolol, timolol, reserpine, indapamide, hydrochlorothiazide, trichloromethiaxide, indacrinone and their analogous drugs.

10 Physical properties and biological activities of certain compounds of this invention will hereinafter be described in the following Referential Examples, Examples and Tests. It should however be borne in mind that the present invention is not limited to the
15 following Examples and Tests. The following Referential Examples relate to the preparation of intermediates for some compounds of the general formula [I], while the following Examples are concerned with the preparation of certain compounds of the general
20 formula [I]. Tests will be described in the [Effects of the Invention].

Referential Example 1:

Methyl 2-(4-benzylpiperazino)-4-
methylpyrimidine-5-carboxylate



One hundred milliliters of a 1 M solution of sodium hydroxide in methanol were added to a suspension (60 ml) of 26.8 g (0.1 mol) of 1-amidino-4-benzyl-piperazine sulfate [which had been synthesized in accordance with the process disclosed in J. Am. Chem. Soc., 66, 263 (1944)] in methanol, followed by a dropwise addition of 15.8 g (0.1 mol) of methyl α -methoxymethyleneacetoacetate. After stirring the resultant mixture overnight at room temperature, the precipitated sodium sulfate was filtered off. After distilling off methanol, the residue was dissolved in 500 ml of ethyl acetate. The resultant solution was washed twice with 100 ml of water. The ethyl acetate layer was washed with saturated saline and then dried with anhydrous magnesium sulfate. Upon distilling off ethyl acetate, 28.7 g of the intended compound was obtained as an orange-colored oily substance (yield: 88%). When the oily substance was left over at room temperature subsequent to its distillation under a reduced pressure, it was crystallized.

Boiling point: 205 - 208°C/1 mmHg.

Melting point: 38 - 40°C.

Infrared absorption spectrum (neat, cm^{-1}):

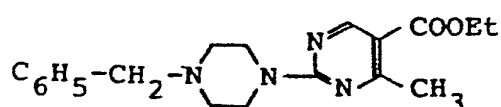
1710, 1580, 1520.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

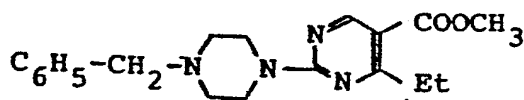
2.50 (4H,m), 2.63 (3H,s), 3.54 (2H,s),
3.83 (3H,s), 3.94 (4H,m), 7.32 (5H,s),
8.78 (1H,s).

5

The following compounds were synthesized in a similar manner.

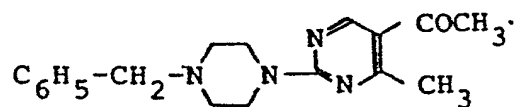


(m.p. 36 - 38.5°C)



(Yellow oil. The raw material was synthesized
by the process of Referential Example 2.)

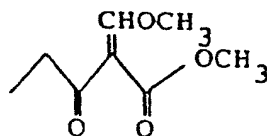
10



(m.p. 85.5 - 87.5°C)

Referential Example 2:

Methyl 2-methoxymethylene-3-oxo-n-valerate



A mixture of 1.95 g of methyl 3-oxo-n-valerate [15 mmol; synthesized in accordance with the process disclosed in J. Am. Chem. Soc., 96, 1082 (1974)], 3.18 g (30 mmol) of methyl orthoformate and
5 4.59 g (45 mmol) of acetic anhydride was heated under reflux for 8 hours, and low b.p. fractions were then distilled off (bath temperature: 100°C). The residue was distilled under reduced pressure to obtain 1.97 g of the intended compound as a yellowish oily substance
10 (yield: 76%). This compound was used in the synthesis of the compound of Referential Example 1.

Boiling point: 86 - 90°C/3 mmHg.

Infrared absorption spectrum (neat, cm^{-1}):

1710, 1625.

15 ^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.07 and 1.08 (total 3H,t,J=7.0Hz),

2.68 and 2.71 (total 2H,q,J=7.0Hz),

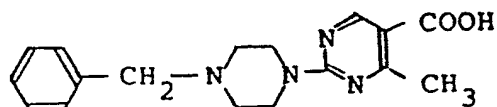
3.74 and 3.81 (total 3H,s),

3.96 and 4.00 (total 3H,s),

20 7.51 and 7.56 (total 1H,s).

Referential Example 3:

2-(4-Benzylpiperazino)-4-methylpyrimidine-5-
carboxylic acid



Added to a 1 l flask were 40 g (0.128 mol) of the ethyl 2-(4-benzylpiperazino)-4-methylpyrimidine-5-carboxylate, 11 g of KOH, 200 ml of H₂O and 500 ml of EtOH. The contents were stirred at 100°C for 0.5
5 hr. Thereafter, the solvent was distilled off under reduced pressure. One liter of H₂O was then added to the residue and the resulting mixture was adjusted to pH 4 with conc. hydrochloric acid. The precipitated crystals were filtered off and the filtrate was dried
10 under reduced pressure, thereby obtaining 36 g of the intended compound as a white solid substance (yield: 98%).

Melting point: 192°C.

Mass spectrum (m/z): 312 (molecular ion peak).

15 Infrared absorption spectrum (KBr tablet, cm⁻¹):

3424, 1700, 1652, 1576.

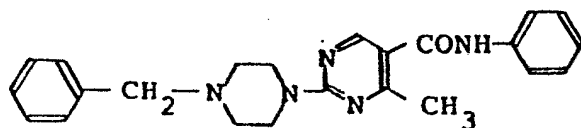
¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

2.56 (3H,s), 2.77 (4H,m), 3.87 (2H,s),

4.00 (4H,m), 7.36 (5H,s), 8.71 (1H,s).

20 Referential Example 4:

2-(4-(Benzylpiperazino)-4-methyl-N-phenyl-
pyrimidine-5-carboxylic acid amide



Added with ice cooling to a suspension (100 ml) of 16.1 g (60 mmol) of 1-amidino-4-benzylpiperazine sulfate in methanol was 100 ml of a methanol solution of 2.4 g (60 mmol) of sodium hydroxide, followed by a dropwise addition of 200 ml of a methanol solution of 14.0 g (60 mmol) of α -ethoxymethyleneacetoacetic anilide (Referential Example 6). After stirring the resultant mixture overnight at room temperature, the precipitated salt was filtered off. The salt was washed with methanol. The filtrate and washing were combined together. After distilling off methanol, the residue was recrystallized from chloroform-hexane to obtain 17.26 g of the intended product as colorless crystals (yield: 74%). This compound was used for the synthesis of the compounds described in Referential Examples 10 and 11.

Melting point: 176 - 177°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

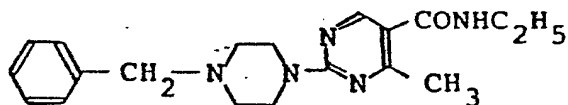
3300, 1653, 1595.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

2.48 (4H,m), 2.53 (3H,s), 3.54 (2H,s),

3.89 (4H,m), 7.1 - 7.6 (5H,m), 7.32 (5H,s),

7.70 (1H,br), 8.39 (1H,s).

Referential Example 5:2-(4-Benzylpiperazino)-N-ethyl-4-methyl-
pyrimidine-5-carboxylic acid amide

Placed in a 50 ml autoclave and reacted at
5 100°C for 3.5 hours were 8.16 g (25 mmol) of the
methyl 2-(4-benzylpiperazino)-4-methylpyrimidine-5-
carboxylate obtained in Referential Example 1, 5.64 g
(125 mmol) of ethyl amine and 1.24 g (5 mmol) of a 21.8
wt.% solution of sodium methoxide in methanol. The
10 thus-obtained reaction mixture was poured in 150 ml of
water, followed by extraction with ethyl acetate. The
ethyl acetate layer was washed with saturated saline
and then dried with magnesium sulfate. Thereafter,
ethyl acetate was distilled off. The residue was
15 recrystallized from ethyl acetate-hexane to obtain 7.71
g of the intended product as light yellowish crystals
(yield: 91%).

Melting point: 110 - 111°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

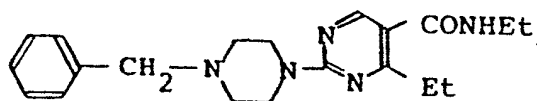
20 3290, 1625, 1585.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

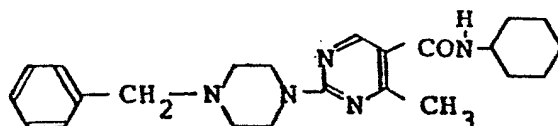
1.22 (3H,t,J=7.0HZ), 2.49 (4H,m), 2.51 (3H,s),
3.42 (2H,m), 3.55 (2H,s), 3.88 (4H,m),

5.76 (1H,m), 7.32 (5H,s), 8.30 (1H,s).

The following compounds were also prepared in a similar manner.

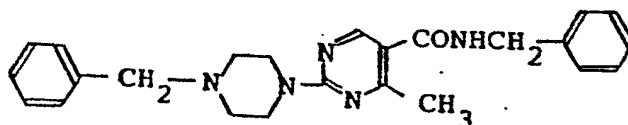


(m.p. 131 - 132°C)



5

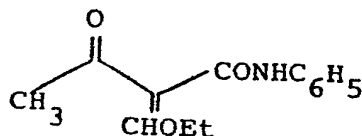
(m.p. 172 - 173°C)



(m.p. 116 - 117°C)

Referential Example 6:

Synthesis of α -ethoxymethyleneacetoacetic anilide



10

A mixture of 26.6 g (0.15 mol) of acetoacetic anilide, 44.5 g (0.3 mol) of ethyl orthoformate and 45.9 g (0.3 mol) of acetic anhydride was heated under

reflux for 2 hours. After cooling the reaction mixture to room temperature, hexane was added. The precipitated crystals were collected by filtration.

Upon their drying, 14.3 g of the intended product was
5 obtained as light brownish needles (yield: 41%).

Melting point: 88 - 89°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

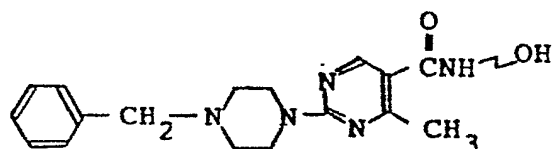
3160, 1660, 1585.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

10 1.46 (3H,t,J=7.0HZ), 2.50 (3H,s),
4.37 (2H,q,J=7.0HZ), 7.0 - 7.77 (6H),
8.46 (1H,s).

Referential Example 7:

15 2-(4-Benzylpiperazino)-N-(2-hydroxyethyl)-
4-methylpyrimidine-5-carboxylic acid amide



Reacted at 170°C for 1.5 hours were 0.34 g (1.0 mmol) of the ethyl 2-(4-benzylpiperazino)-4-methylpyrimidine-5-carboxylate and 1.22 g (20 mmol) of ethanol amine. After adding 50 ml of water, the
20 resultant mixture was extracted with ethyl acetate. After washing the ethyl acetate layer with saturated saline, the ethyl acetate solution was dried with magnesium sulfate. Ethyl acetate was distilled off

under reduced pressure and upon recrystallization of the residue from ethyl acetate-hexane, 0.25 g of the intended product was obtained as white crystals (yield: 72%).

5 Melting point: 123°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

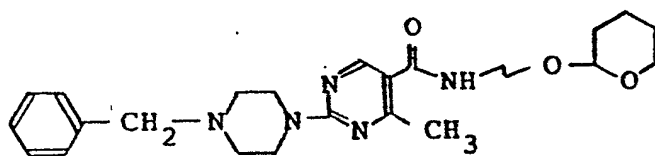
3280, 1630, 1594.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

2.48 (4H, m), 2.51 (3H, s), 2.46 - 2.62 (4H, m),
10 2.73 - 2.83 (6H, m), 6.39 (1H, brs), 7.32 (5H, s),
8.35 (1H, s).

Referential Example 8:

15 2-(4-Benzylpiperazino)-4-methyl-N-[2-(2'-tetrahydropyranyloxy)ethyl]pyrimidine-5-carboxylic acid amide



To an ethyl acetate solution (160 ml) of 2.76 g (7.75 mmol) of the 2-(4-benzylpiperazino)-N-(2-hydroxyethyl)-4-methylpyrimidine-5-carboxylic acid amide obtained in Referential Example 7, 6.52 g (77.5 mmol) of 2,3-dihydropyran and 1.77 g (9.30 mmol) of p-toluenesulfonic acid monohydrate were added. The resultant mixture was stirred at room temperature for 2 days. The thus-obtained reaction mixture was washed

with a saturated solution of sodium bicarbonate and was then dried with magnesium sulfate. Thereafter, ethyl acetate was distilled off under reduced pressure. The residue was purified by silica gel chromatography (eluent: ethyl acetate), thereby obtaining 3.24 g of the intended product as light yellowish crystals (yield: 95%).

Melting point: 87 - 88°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

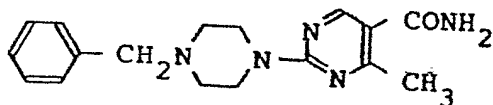
3280, 1622, 1588.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.3 - 2.0 (6H), 2.48 (4H,m), 2.52 (3H,s),
3.54 (2H,s), 3.5 - 3.9 (6H), 3.89 (4H,m),
4.56 (1H,m), 6.54 (1H,m), 7.31 (5H,s),
8.35 (1H,s).

Referential Example 9:

2-(4-Benzylpiperazino)-4-methyl-pyrimidine-5-carboxylic acid amide



To 80 ml of pyridine containing, in a suspended state, 4.69 g (15 mmol) of the 2-(4-benzylpiperazino)-4-methylpyrimidine-5-carboxylic acid obtained in Referential Example 3, 4.45 g (37.5 mmol) of SOCl_2 was added. The resultant mixture was stirred at room

temperature for 1 hour. Thereafter, 2.2 g (37.5 mmol) of 30% aqueous ammonia solution was added and the resultant mixture was stirred overnight at room temperature. After distilling off pyridine from the reaction mixture under reduced pressure, 200 ml of water was added, the pH of the resultant mixture was adjusted with K_2CO_3 to pH 8, and the thus-treated mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated saline. After drying the ethyl acetate solution with magnesium sulfate, ethyl acetate was distilled off under reduced pressure. The residue was recrystallized from chloroform-hexane to obtain 1.17 g of the intended product (yield: 25%).

Melting point: 195 - 196°C.

Mass spectrum (m/z): 311 (molecular ion peak).

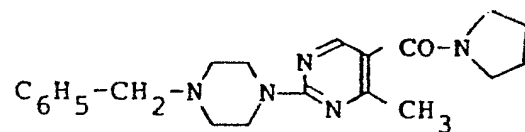
Infrared absorption spectrum (KBr tablet, cm^{-1}):

3497, 3367, 1611, 1577.

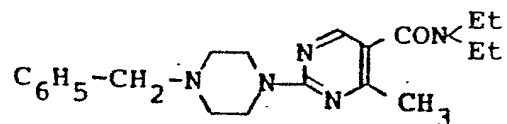
1H -NMR spectrum ($CDCl_3$ solution, δ ppm):

2.48 (4H,m), 2.56 (3H,s), 3.54 (2H,s),
3.90 (4H,m), 7.31 (5H,s), 8.43 (1H,s).

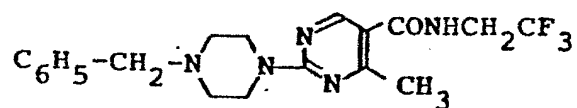
The following compounds were also synthesized in a similar manner:



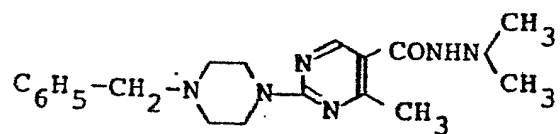
(m.p. 164 - 165°C)



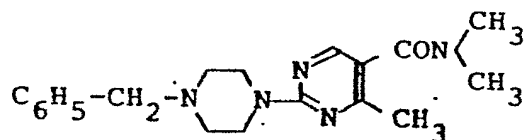
(m.p. 121 - 122°C)

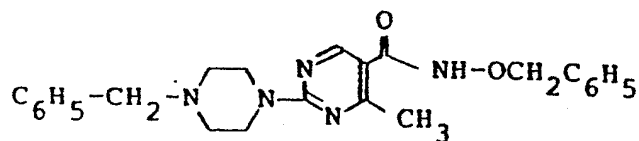


(m.p. 156 - 157°C)

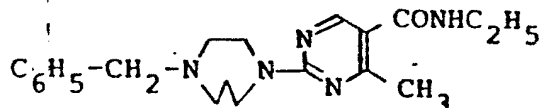


(m.p. 157 - 158°C)





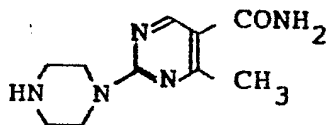
(m.p. 150 - 151°C)



(The raw material was obtained in Referential Example 78.)

Referential Example 10:

5 4-Methyl-2-piperazino-N-tetramethylene-
pyrimidine-5-carboxylic acid amide



Placed in a two-necked 100 ml flask were 1.00 g of the 2-(4-benzylpiperazino)-4-methyl-N-tetramethylenepyrimidine-5-carboxylic acid amide obtained in
 10 Referential Example 9 and 0.1 g of 10% Pd-C, followed by hydrogen substitution under reduced pressure. Then, 20 ml of absolute ethanol and 20 ml of glacial acetic acid were added and the resultant mixture was stirred at 60 - 65°C, under normal pressure for 1 hour. The
 15 reaction mixture was filtered and the catalyst was washed with ethanol. The filtrate was distilled to

dryness under reduced pressure to obtain a viscous oily substance. The oily substance was purified by silica gel column chromatography (developed with EtOH), thereby obtaining 0.70 g of colorless crystals (yield: 93%).

5 Melting point: 228°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

3420, 3300, 1625, 1585.

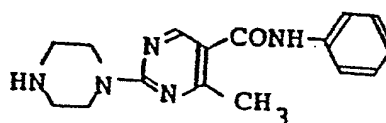
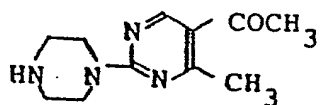
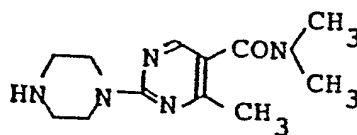
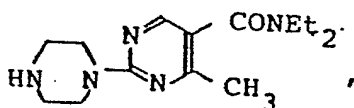
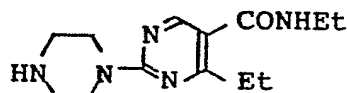
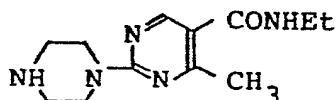
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

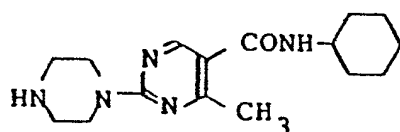
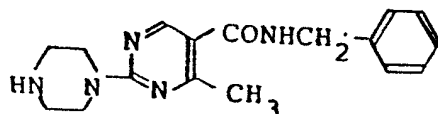
1.82 (4H,br), 2.25 (3H,s), 2.73 (4H,m),

10

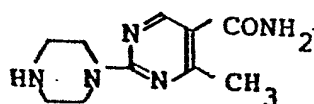
3.3 (4H,m), 3.70 (4H,m), 8.20 (1H,s).

The following compounds were also synthesized in a similar manner.

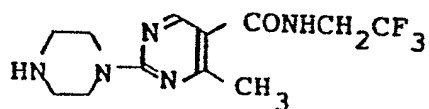




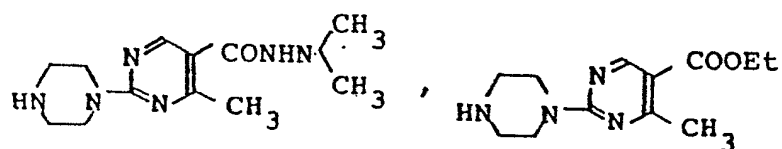
(m.p. 180 - 182°C)



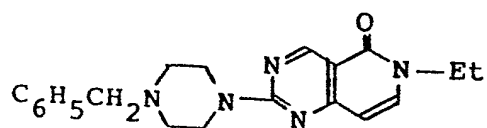
(m.p. 210 - 212°C)



(m.p. 148 - 150°C)

Referential Example 11:

6-Ethyl-2-(4-benzylpiperazino)pyrido[4,3-d]-
pyrimidin-5(6H)-one



After washing 240 mg of sodium hydride (60% in oil, 6 mmol) with hexane, it was suspended in 3 ml of N,N-dimethylformamide (DMF). Thereafter, a DMF solution (10 ml) of 1.7 g (5 mmol) of 2-(4-benzyl-
5 piperazino)-N-ethyl-4-methylpyrimidine-5-carboxylic acid amide (Referential Example 5) was added and the reactants were reacted at 150°C for 1.5 hours. After distilling off DMF under reduced pressure, 100 ml of water was added, followed by extraction with ethyl
10 acetate. The ethyl acetate layer was washed with saturated saline and dried with magnesium sulfate, and ethyl acetate was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to obtain 1.5 g of the intended product as light
15 yellowish crystals (yield: 87%).

Melting point: 116 - 118°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

1660, 1638.

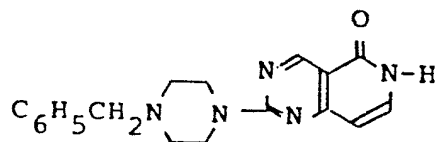
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

20 1.32 (3H,t,J=7HZ), 2.50 (4H,t,J=6HZ),
3.54 (2H,s), 3.76 - 4.08 (6H,m),
6.24 (1H,d,J=7HZ), 7.23 (1H,d,J=7HZ),
7.31 (5H,s), 9.20 (1H,s).

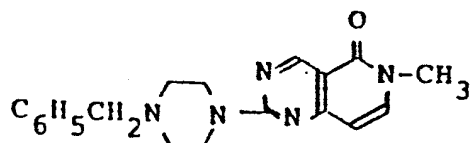
The following compounds were also synthesized in
25 a similar manner.

0188094

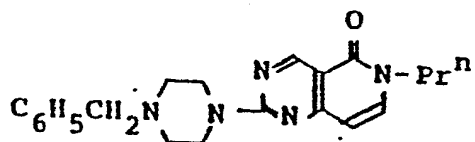
- 39 -



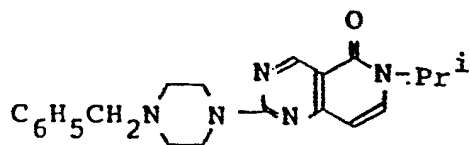
(m.p. 201°C)



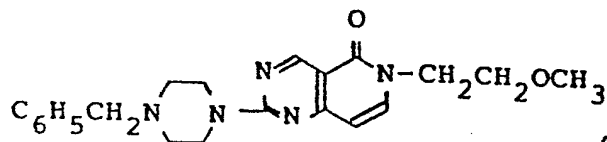
(viscous liquid)



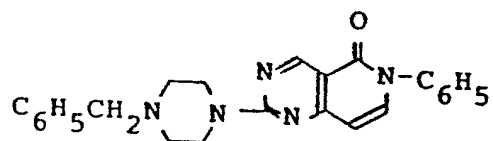
(light yellowish oil)



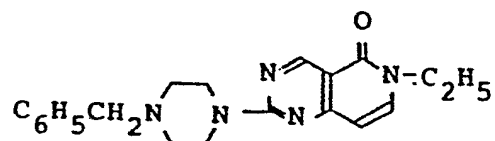
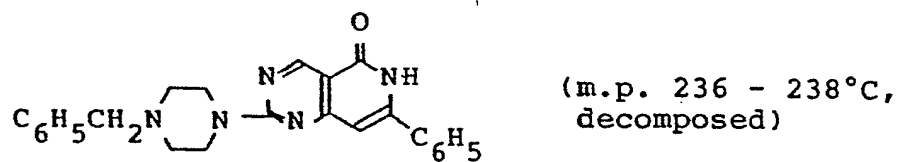
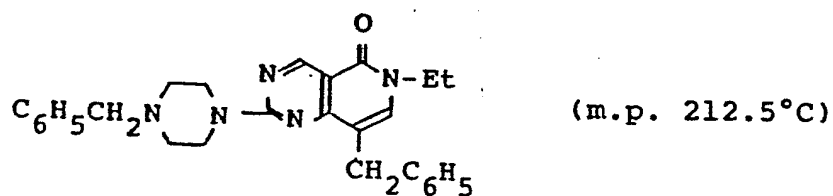
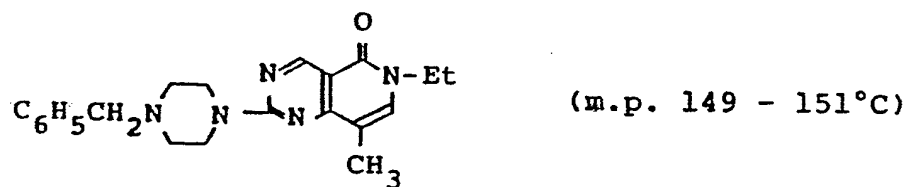
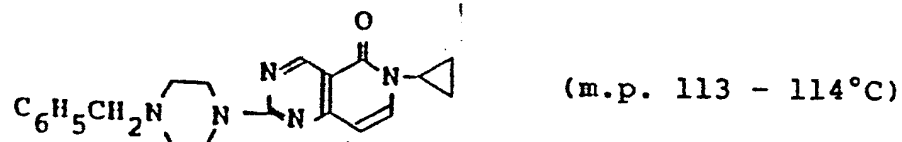
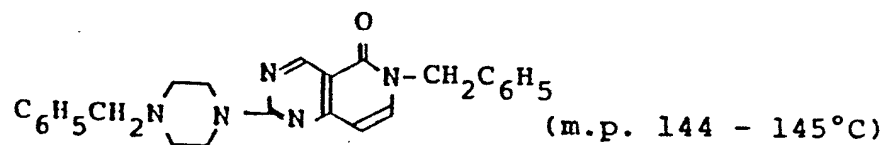
(m.p. 157°C)



(oil)

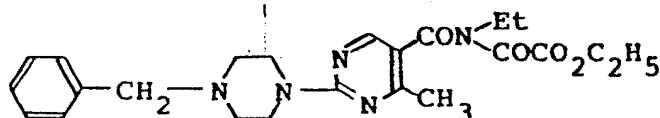


(m.p. 167 - 168°C)



Referential Example 12:

2-(4-Benzylpiperazino)-N-ethyl-N-ethyl-
oxaloyl-4-methylpyrimidine-5-carboxylic
acid amide



5 Five milliliters of a tetrahydrofuran solution
of 0.335 g (1 mmol) of the 2-(4-benzylpiperazino)-N-
ethyl-4-methylpyrimidine-5-carboxylic acid amide
obtained in Referential Example 5 were cooled in an ice
bath, to which 0.048 g (60% in oil, 1.2 mmol) of sodium
10 hydride was added. The resultant mixture was stirred
for 10 minutes. Thereafter, 1 ml of a tetrahydrofuran
solution of 0.15 g (1.1 mmol) of ethyloxalyl chloride
was added dropwise. The thus-prepared mixture was
stirred at room temperature for 1 hour and then at
15 70°C for further 4 hours. The thus-obtained reaction
mixture was poured in 50 g of ice water, followed by
extraction with ethyl acetate. The organic layer was
washed with saturated saline and then dried with sodium
sulfate. Thereafter, the solvent was distilled off
20 under reduced pressure. The residue was purified by
silica gel column chromatography (eluent: ethyl
acetate/hexane = 3/2) to obtain 0.306 g of the intended
product as a light blue oil (yield: 71%).

Infrared absorption spectrum (neat, cm^{-1}):

1740, 1712, 1672, 1590.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

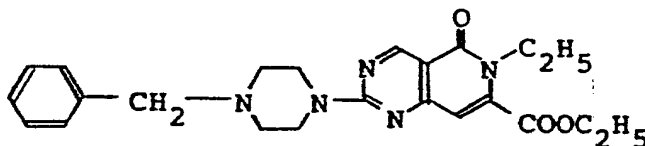
1.18 (3H,t,J=7.2Hz), 1.24 (3H,t,J=7.2Hz),

5 2.47 (3H,s), 2.51 (4H,m), 3.58 (2H,s),

3.72 - 4.16 (8H,m), 7.34 (5H,s), 8.23 (1H,s).

Referential Example 13:

Ethyl 2-(4-benzylpiperazino)-5,6-dihydro-
6-ethyl-5-oxopyrido[4,3-d]pyrimidine-7-
 10 carboxylate



A mixture of 0.3 g (0.68 mmol) of the 2-(4-benzylpiperazino)-N-ethyl-N-ethyloxaloyl-4-methylpyrimidine-5-carboxylic acid amide obtained in Referential Example 12, 0.027 g (60% in oil, 0.68 mmol)
 15 of sodium hydride and 5 ml of dimethylformamide was reacted at 120°C for 2 hours. Fifty grams of ice water were added, followed by extraction with ethyl acetate. The oil layer was washed with saturated saline and was then dried with sodium sulfate. Ethyl
 20 acetate was distilled off under reduced pressure and the residue was purified by silica gel column chromatography (eluent: ethyl acetate), thereby

obtaining 0.095 g of a light yellowish oil (yield: 33%). This compound was used for the preparation of the compound described in Referential Example 14.

Infrared absorption spectrum (neat, cm^{-1}):

5 1730, 1660, 1613, 1574.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

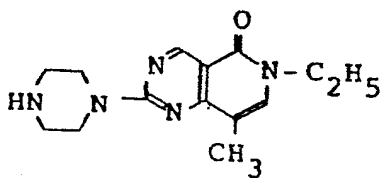
1.35 (3H,t,J=7Hz), 1.42 (3H,t,J=7Hz),
2.51 (4H,t,J=5.5Hz), 3.55 (2H,s),
3.98 (4H,t,J=5.5Hz), 4.26 (2H,q,J=7Hz),
10 4.40 (2H,q,J=7Hz), 6.75 (1H,s), 7.37 (5H,s),
9.22 (1H,s).

Mass spectrum:

421 (molecular ion peak).

Referential Example 14:

15 5,6-Dihydro-6-ethyl-8-methyl-5-oxo-2-
piperazinopyrido[4,3-d]pyrimidine-5(6H)-one



Added to 300 mg (0.83 mmol) of the 2-(4-benzyl-piperazino)-6-ethyl-8-methylpyrido[4,3-d]pyrimidine-5(6H)-one obtained in Referential Example 11 were 6 ml
20 of ethanol, 2 ml of acetic acid and 30 mg of 10% Pd-C. The resultant mixture was stirred at 45°C for 3.5 hours in a hydrogen atmosphere. The Pd-C was removed

from the reaction mixture, followed by concentration under reduced pressure. The concentrate was added with 20 ml of water, to which potassium carbonate was added until no foams were developed. The resultant mixture
 5 was extracted three times with 50 ml of chloroform. The chloroform layer was dried with sodium sulfate and then concentrated under reduced pressure, thereby obtaining 200 mg of 6-ethyl-8-methyl-2-piperazino-
 pyrido[4,3-d]pyrimidine-5(6H)-one as colorless crystals
 10 (yield: 88%).

Melting point: 170 - 172°C.

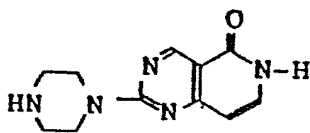
Infrared absorption spectrum (KBr tablet, cm^{-1}):

1657, 1618, 1578.

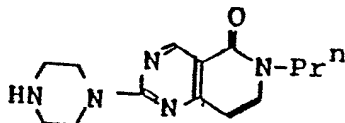
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

15 1.33 (3H,t,J=7.2Hz), 1.66 (1H,s),
 2.17 (3H,d,J=1.3Hz), 2.94 (4H,m), 3.97 (6H,m),
 7.10 (1H,q,J=1.3Hz), 9.24 (1H,s).

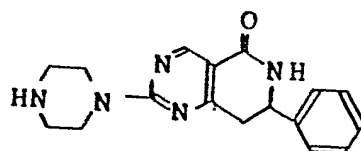
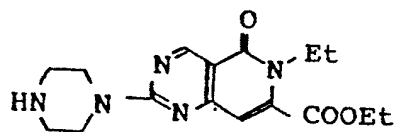
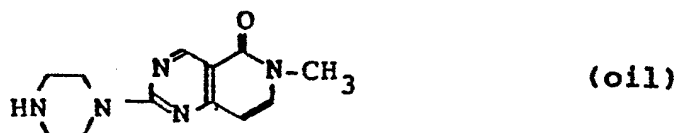
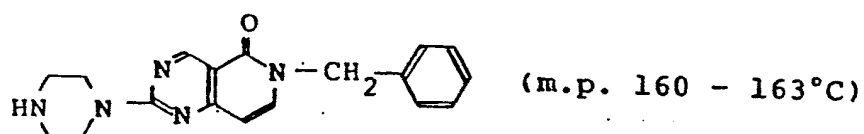
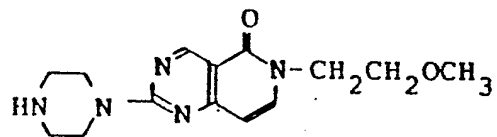
The following compounds were also prepared in a similar manner.

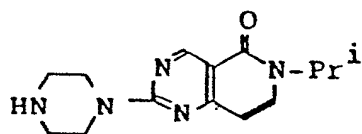


(m.p. 252.8°C)

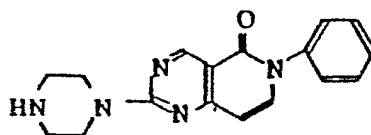


(m.p. 143°C)

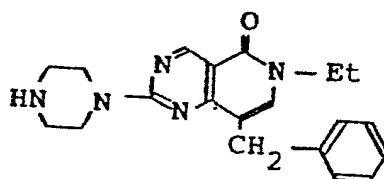
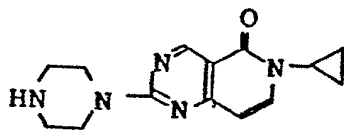




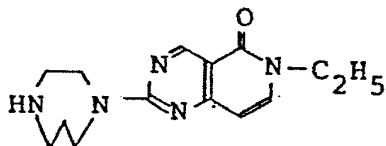
(m.p. 161°C)



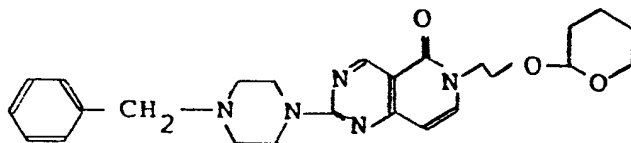
(m.p. 100 - 105°C)



(m.p. 231.7°C)

Referential Example 15:

2-(4-Benzylpiperazino)-6-(2-(2'-tetrahydro-
pyranyloxy)ethyl)pyrido[4,3-d]pyrimidine-
5(6H)-one



After washing 240 mg of sodium hydride (60% in oil, 6 mmol) with hexane, it was suspended in 2 ml of DMF. Thereafter, a DMF solution (10 ml) of 1.76 g (3 mmol) of 2-(4-benzylpiperazino)-4-methyl-N-(2-(2'-
5 tetrahydropyranyloxy)ethyl)pyrimidine-5-carboxylic acid amide (Referential Example 8) was added. The resultant mixture was stirred at 150°C for 7 hours. After driving off DMF under reduced pressure, 100 ml of water was added, followed by extraction with ethyl
10 acetate. The ethyl acetate layer was washed with saturated saline and dried with MgSO_4 , and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.86 g
15 of the intended product as a yellowish oily substance (yield: 64%).

Infrared absorption spectrum (neat, cm^{-1}):

1650, 1615, 1573, 1540, 1505.

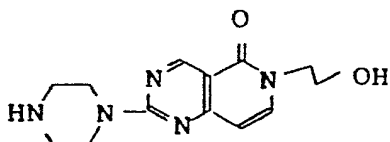
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

20 1.3 - 2.0 (6H,m), 2.52 (4H,m), 3.56 (2H,s),
3.4 - 4.3 (10H, m), 4.56 (1H, m),
6.26 (1H,d,J=7.4Hz), 7.33 (5H,s),

7.40 (1H,d,J=7.4Hz), 9.22 (1H,s).

Referential Example 16:

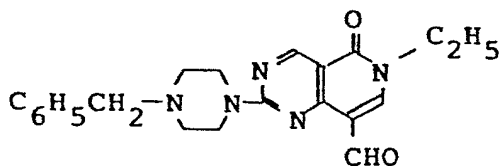
2-Piperazino-6-(2-hydroxyethyl)pyrido-
[4,3-d]pyrimidine-5(6H)-one



- 5 An ethanol-acetic acid solution [15 ml,
ethanol/acetic acid = 2 (volume ratio) of 450 mg (1
mmol) of the 2-(4-benzylpiperazino)-6-(2(2'-tetra-
hydropyranyloxy)ethyl)pyrido[4,3-d]pyrimidine-5(6H)-one
obtained in Referential Example 15 was added with 10%
10 Pd-C, to which hydrogen was introduced under
atmospheric pressure at 80°C for 6.5 hours to effect
debenzylation. After the reaction, the catalyst was
filtered off and the filtrate was concentrated under
reduced pressure to obtain the above-identified
15 compound.

Referential Example 17:

2-(4-Benzylpiperazino)-5,6-dihydro-6-ethyl-
5-oxopyrido[4,3-d]pyrimidine-8-carbaldehyde



Dissolved in 4.0 ml of diethylformamide was 0.4 g of the 2-(4-benzylpiperazino)-4-methylpyrimidine-5-carboxylic acid obtained in Referential Example 3. At room temperature, 0.5 ml of phosphorus oxychloride was added dropwise. Thereafter, the contents were heated and reacted at 100°C for 1.5 hours. After cooling, the reaction mixture was poured in an aqueous solution of sodium carbonate to neutralize same, followed by extraction with chloroform. After washing the chloroform layer with water, it was dried with anhydrous magnesium sulfate. Chloroform was distilled off under reduced pressure to obtain 0.29 g of the intended product (yield: 60%).

Melting point: 151.9°C.

Mass spectrum: 377 (molecular ion peak).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

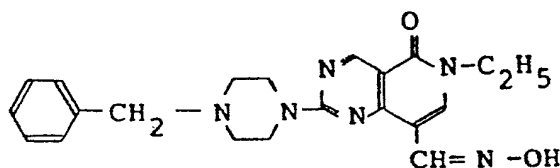
1690, 1662, 1628, 1570.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.39 (3H,t,J=7Hz), 2.52 (4H,m), 3.58 (2H,s),
4.02 (4H,m), 4.05 (2H,q,J=7Hz), 7.33 (5H,s),
8.18 (1H,s), 9.19 (1H,s), 10.33 (1H,s).

Referential Example 18:

2-(4-Benzylpiperazino)-5,6-dihydro-6-ethyl-
5-oxopyrido[4,3-d]pyrimidine-8-carbaldehydo-
oxime



Dissolved in dimethylsulfoxide was 3.0 g of the 2-(4-benzylpiperazino)-5,6-dihydro-6-ethyl-5-oxopyrido-[4,3-d]pyrimidine-8-carbaldehyde obtained in Referential Example 17. The solution was heated to 50°C, at which an aqueous solution (10 ml) containing 0.83 g of hydroxylamine hydrochloride and 0.7 g of potassium hydroxide was added dropwise. Thereafter, the contents were stirred and reacted for further 30 minutes. The reaction mixture was poured in water, and the precipitate was collected by filtration and then washed with methanol. It was dried under reduced pressure to obtain 2.65 g of light yellowish crystals (yield: 82%).

Melting point: 226.6 °C.

Mass spectrum: 392 (molecular ion peak).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

3355, 3174, 1654, 1645, 1582.

^1H -NMR spectrum (DMSO- d_6 solution, δ ppm):

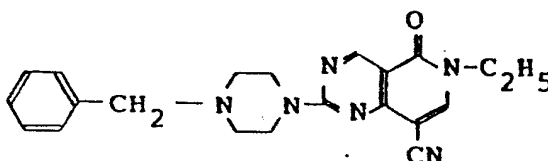
1.32 (3H,t,J=7Hz), 2.56 (4H,brs), 3.62 (2H,s),

3.80 - 4.10 (6H,m), 7.32 (5H, s), 8.06 (1H,s),

8.42 (1H,s), 9.06 (1H,s), 10.87 (1H,s).

Referential Example 19:

Preparation of 2-(4-benzylpiperazino)-5,6-
dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidine-
carbonitrile



Added to 100 g of phosphorus oxychloride was
5 3.13 g of the 2-(4-benzylpiperazino)-5,6-dihydro-6-
ethyl-5-oxopyrido[4,3-d]pyrimidine-8-carbaldehydoxime
obtained in Referential Example 18. The resultant
mixture was heated under reflux for 0.5 hr. Excess
phosphorus oxychloride was distilled off. Chloroform
10 and a 10% aqueous solution of sodium hydroxide were
added to the reaction mixture to neutralize same,
followed by extraction with chloroform. The chloroform
layer was dried with anhydrous magnesium sulfate.
Chloroform was distilled off under reduced pressure and
15 the extract was recrystallized from toluene, thereby
obtaining 2.2 g of light yellowish crystals (yield:
74%).

Melting point: 218.3°C.

Mass spectrum: 374 (molecular ion peak).

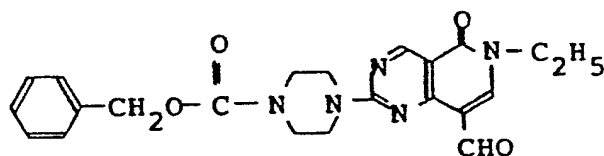
20 ¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.39 (3H,t,J=7Hz), 2.53 (4H,m), 3.57 (2H,s),
3.90 - 4.20 (6H,m), 7.33 (5H,s), 7.87 (1H,s),

9.15 (1H,s).

Referential Example 20:

2-(4-Benzylloxycarbonylpiperazino)-5,6-dihydro-
6-ethyl-5-oxopyrido[4,3-d]pyrimidine-8-
5 carbaldehyde



Dissolved in 5.0 ml of tetrahydrofuran was 0.55 g of the 2-(4-benzylpiperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidine-8-carbaldehyde obtained in Referential Example 17, to which 0.31 g of benzyl
10 chlorocarbonate was added dropwise at room temperature. The resultant mixture was stirred at 50°C for further 3 hours. After allowing the reaction mixture to cool, tetrahydrofuran was distilled off under reduced pressure and the residue was washed with n-hexane to
15 obtain 0.55 g of light yellowish crystals (yield: 91%). Melting point: 208.0 - 208.9°C.

Mass spectrum: 421 (molecular ion peak).

Infrared absorption spectrum (nujol, cm^{-1}):

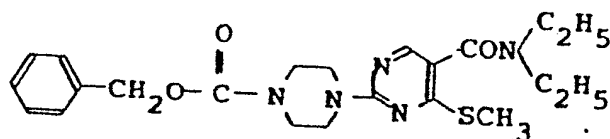
1711, 1691, 1657.

20 ^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.41 (3H,t,J=7Hz), 3.62 (4H,m), 4.01 (6H,m),
5.20 (2H,s), 7.38 (5H,s), 8.23 (1H,s),

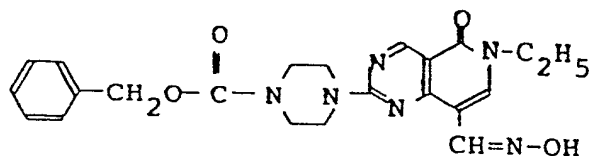
9.24 (1H,s), 10.56 (1H,s).

The following compound was synthesized in the same manner except that the reaction was carried out at 50°C for 12 hours by using 2-(4-benzyl-piperazino)-4-methylthiopyrimidine-5-carboxylic acid diethylamide
 5 obtained in Referential Example 68 in place of 2-(4-benzylpiperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidine-8-carbaldehyde.



Referential Example 21:

10 2-(4-Benzylloxycarbonylpiperazino)-5,6-dihydro-
 6-ethyl-5-oxopyrido[4,3-d]pyrimidine-8-
 carbaldehydoxime



Dissolved in 20 ml of chloroform was 1.0 g of the 2-(4-benzylloxycarbonylpiperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidine-8-carbaldehyde
 15 obtained in Referential Example 20, to which an aqueous solution of 0.25 g of hydroxylamine hydrochloride and 0.24 g of potassium hydroxide was added at room

temperature. Thereafter, the resulting mixture was heated with stirring at 60°C for 2.5 hours. After allowing the reaction mixture to cool down, the chloroform layer was collected and dried with anhydrous magnesium sulfate. Chloroform was distilled off under reduced pressure and the resultant crude crystals were washed with n-hexane to obtain 0.81 g of light yellowish crystals (yield: 81%).

Melting point: 170.9°C.

10 Mass spectrum: 436 (molecular ion peak).

Infrared absorption spectrum (nujol, cm^{-1}):

1645, 1583, 1491, 1348.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

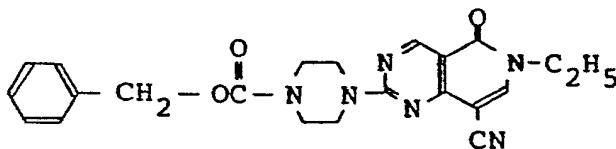
1.37 (3H,t,J=7.0Hz), 3.61 (4H,m), 3.96 (6H,m),

15 5.19 (2H,s), 7.36 (5H,s), 7.93 (1H,s),

8.61 (1H,s), 9.25 (1H,s).

Referential Example 22:

2-(4-Benzoyloxypiperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidine-8-carbonitrile



The above-identified compound was synthesized in the same manner as in Referential Example 20 except

that the reaction was carried out at room temperature for 12 hours by using 2-(4-benzylpiperazino)-5,6-dihydro-6-ethyl-5-oxo[4,3-d]pyrimidine-8-carbonitrile (Referential Example 19) instead of 2-(4-benzyl-
5 piperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]-pyrimidine-8-carbaldehyde (slightly yellowish crystals, yield: 79%).

Melting point: 184 - 186°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

10 2239 (CN), 1709, 1662, 1623, 1580.

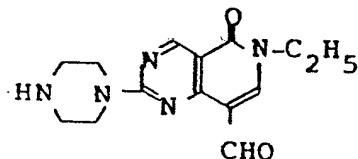
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.40 (3H,t,J=7.2Hz), 3.60 (4H,m), 4.10 (6H,m),
5.20 (2H,s), 7.39 (5H,s), 7.89 (1H,s),
9.20 (1H,s).

15 Incidentally, the present compound may also be synthesized by dehydrating the compound of Referential Example 21 in the same manner as in Referential Example 19.

Referential Example 23:

20 5,6-Dihydro-6-ethyl-5-oxo-2-piperazinopyrido-
[4,3-d]pyrimidine-8-carbaldehyde



Dissolved in a 25% hydrogen bromide solution of acetic acid was 0.2 g of the 2-(4-benzyloxycarbonyl-piperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]-pyrimidine-8-carbaldehyde obtained in Referential

5 Example 20. The resulting mixture was stirred at room temperature for 1 hour. Hydrogen bromide, acetic acid and resulting benzyl bromide were distilled off under reduced pressure. After neutralizing the residue with a saturated aqueous solution of sodium carbonate, the
10 mixture was extracted with chloroform and the chloroform layer was dried with anhydrous magnesium sulfate. Chloroform was distilled off under reduced pressure to obtain 0.13 g of light yellowish crystals (yield: 95%).

15 Melting point: over 300°C.

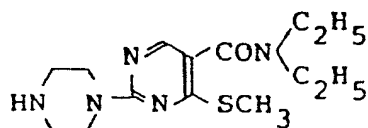
Infrared absorption spectrum (nujol, cm^{-1}):

3400, 1688, 1655.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

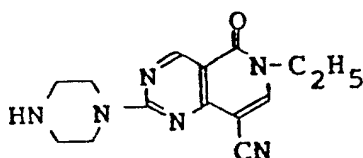
1.40 (3H,t,J=7.0Hz), 2.95 (4H,m), 4.08 (6H,m),
20 8.19 (1H,s), 9.20 (1H,s), 10.55 (1H,s).

The following compound was also synthesized in a similar manner. (The raw material was synthesized in Referential Example 20.)



Referential Example 24:

5,6-Dihydro-6-ethyl-5-oxo-2-piperazinopyrido-
[4,3-d]pyrimidine-8-carbonitrile



To 0.4 g of the 2-(4-benzyloxycarbonyl-
 5 piperazino)-5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]-
 pyrimidine-8-carbonitrile obtained in Referential
 Example 22, 15 ml of ethanol, 1 ml of acetic acid and
 0.2 g of 5% Pd-C were added. The resulting mixture was
 stirred at 50°C for 2 hours in a hydrogen atmosphere
 10 of normal pressure. Pd-C was removed from the reaction
 mixture by filtration and the resultant filtrate was
 concentrated under reduced pressure. The concentrate
 was added with 20 ml of water and 1 ml of 2M-HCl and
 then washed with chloroform. The water layer was
 15 neutralized with potassium carbonate and then extracted
 with chloroform. The chloroform solution was dried
 with anhydrous sodium sulfate and chloroform was then

driven off under reduced pressure, thereby obtaining 80 mg of slightly yellowish crystals (yield: 29%).

Melting point: 204 - 206°C (decomposed).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

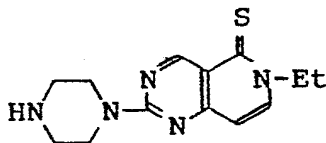
5 2230 (CN), 1671, 1620, 1578.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.40 (3H,t,J=7.2Hz), 1.65 (1H,s), 2.95 (4H,m),
4.00 (6H,m), 7.88 (1H,s), 9.19 (1H,s).

Referential Example 25:

10 5,6-Dihydro-6-ethyl-5-thioxo-2-piperazino-
pyrido[4,3-d]pyrimidine



In pyridine (20 ml), 2 g (7.7 mmol) of the 5,6-dihydro-6-ethyl-5-oxo-2-piperazinopyrido[4,3-d]-pyrimidine obtained in Referential Example 14 and 6 g
15 (27 mmol) of phosphorus pentasulfide were reacted at 100°C for 3 hours. Thereafter, pyridine was distilled off under reduced pressure and the residue was taken up in hot water. The resultant aqueous solution was extracted with chloroform. The chloroform layer was
20 dried with anhydrous magnesium sulfate, followed by its concentration. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol =

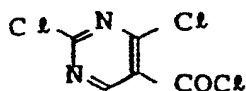
95/5) to obtain 0.3 g of the intended product (yield: 14%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.44 (3H,t,J=7.0Hz), 3.52 (4H,m), 3.98 (2H,m),
4.38 (4H,m), 6.58 (1H,d,J=7.5Hz),
7.55 (1H,d,J=7.5Hz), 9.79 (1H,s).

Referential Example 26:

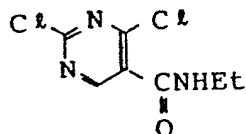
2,4-Dichloro-5-chlorocarbonylpyrimidine



Twenty grams of 2,4-dihydroxypyrimidine-5-carboxylic acid and 220 ml of phosphorus oxychloride were reacted under reflux for 10 hours. Thereafter, the reaction mixture was cooled to room temperature and 100 g of phosphorus pentachloride was added. The contents were again reacted at 120°C for 7 hours. After completion of the reaction, phosphorus oxychloride was distilled off and the reaction product was purified by its distillation under reduced pressure (b.p. 130 - 140°C/1 mmHg, yield: 35%).

Referential Example 27:

2-4-Dichloro-N-ethyl-5-carboxylic acid amide



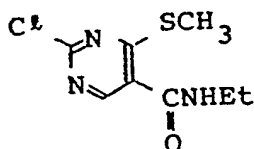
To a solution of 1.02 g (4.8 mmol) of the 2,4-dichloro-5-chlorocarbonylpyrimidine synthesized in Referential Example 26 in methylene chloride (5 ml), 0.6 ml of ethylamine was added at -20°C. The resultant mixture was then reacted at room temperature for 2 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. After drying the methylene chloride layer with magnesium sulfate, methylene chloride layer was distilled off under reduced pressure to obtain 0.97 g of the intended product as yellowish solid (yield: 91%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.28 (3H,t,J=7.2Hz), 3.52 (2H,m), 8.92 (1H,s).

Referential Example 28:

15 2-Chloro-N-ethyl-4-methylthio-5-carboxylic acid amide



An NaSCH₃/MeOH solution, which had been prepared on the side, was added dropwise to 1.15 g (5.2

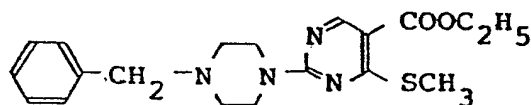
mmol) of the 2,4-dichloro-N-ethyl-5-carboxylic acid
amide prepared in Referential Example 27. Reaction
course was monitored by TLC. Upon consumption of the
raw material, the reaction mixture was concentrated and
5 was then added with water, followed by extraction with
chloroform. The chloroform layer was dried with
anhydrous magnesium sulfate. Under reduced pressure,
chloroform was distilled off. The residue was purified
by silica gel column chromatography to obtain 0.7 g of
10 the intended product (yield: 54%).

Melting point: 188 - 190°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

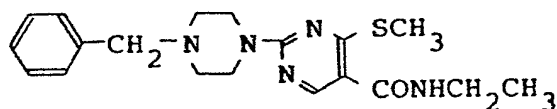
1.27 (3H,t,J=7.4Hz), 2.59 (3H,s),
3.50 (2H,d,q,J=5.7 and 7.4Hz), 6.12 (1H,br.t),
15 8.47 (1H,s).

The following compound was synthesized in the
same manner except that the ethyl 2-(4-benzyl-
piperazino)-4-chloropyrimidine-5-carboxylate obtained
in Referential Example 63 was used in place of 2,4-
20 dichloro-N-ethyl-5-carboxylic acid amide.



Referential Example 29:

2-(4-Benzylpiperazino)-N-ethyl-4-methylthio-

5-carboxylic acid amide

One milliliter of benzylpiperazine was added to 10 ml of a butanol solution in which 1.0 g of the 2-chloro-N-ethyl-4-methylthio-5-carboxylic acid amide synthesized in Referential Example 28 was dissolved. The resultant mixture was refluxed for 2 hours. The reaction mixture was cooled, the precipitated benzylpiperazine hydrochloride was filtered off, and the filtrate was then concentrated under reduced pressure. The concentrate was recrystallized from ethyl acetate, thereby obtaining 600 mg of the intended product as colorless crystals (yield: 41%).

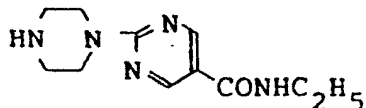
Melting point: 145 - 148°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.23 (3H,t,J=7.2Hz), 2.46 (3H,s),
2.56 (4H,m), 3.46 (2H,d,q,J=5.7 and 7.2Hz),
3.55 (2H,s), 3.90 (4H,m), 6.20 (1H,br.t),
8.36 (1H,s).

Referential Example 30:

N-Ethyl-2-piperazino-5-carboxylic acid amide

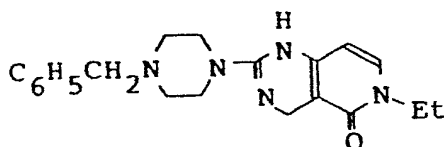


An ethanol solution (10 ml) of 100 mg of the 2-(4-benzylpiperazino)-N-ethyl-4-methylthio-5-carboxylic acid amide synthesized in Referential Example 29 was added with 500 mg of Raney nickel and was then refluxed for 2.5 hours. Raney nickel was filtered off from the reaction mixture and the filtrate was concentrated under reduced pressure. The concentrate was added with 10 ml of methylene chloride and 1 ml of water. The resultant mixture was then allowed to separate into layers. After drying the methylene chloride layer with anhydrous sodium sulfate, it was concentrated to obtain 40 mg of the intended product as a colorless oil (yield: 64%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):
1.23 (3H,t,J=7.0Hz), 2.95 (4H,m),
3.45 (2H,d.q,J=5.3 and 7.0Hz), 3.85 (4H,m),
6.20 (1H,br.t), 8.71 (2H,s).

Referential Example 31:

1,4,5,6-Tetrahydro-6-ethyl-5-oxo-2-(4-benzylpiperazino)pyrido[4,3-d]pyrimidine



Added at room temperature to a suspension of
0.80 (21 mmol) of lithium aluminum hydride in THF (20
ml) was 1.5 g of 5,6-dihydro-6-ethyl-5-oxo-2-(4-
benzylpiperazino)pyrido[4,3-d]pyrimidine (Referential
5 Example 11). After refluxing the reaction mixture for
4 hours, the reaction mixture was added with water to
decompose excess lithium aluminum hydride. An aqueous
solution of sodium hydroxide and chloroform were added
to the resultant mixture to extract the latter. After
10 washing the chloroform layer with water, it was dried
with anhydrous magnesium sulfate and was then
concentrated to obtain 1.4 g of light yellowish
crystals. The crude crystals were immersed in ethyl
acetate to obtain 1.1 g of 1,4,5,6-Tetrahydro-6-ethyl-
15 5-oxo-2-(4-benzylpiperazino)pyrido[4,3-d]pyrimidine as
colorless crystals (yield: 72%).

Melting point: 200 - 203°C.

Mass spectrum: 351 (M^+).

Infrared absorption spectrum (CHCl_3 solution, cm^{-1}):

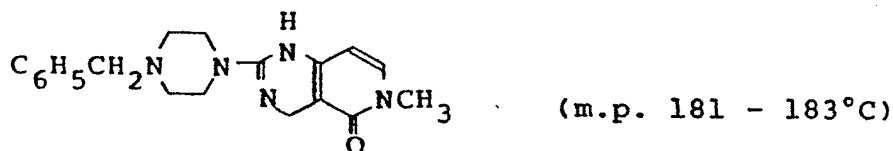
20 1640, 1565, 1529.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.30 (3H, t, $J=7\text{Hz}$), 2.50 (4H, m),

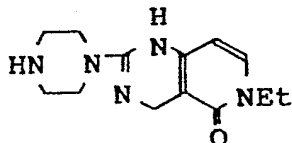
3.54 (6H,m), 3.90 (2H,q,J=7Hz), 4.42 (2H,s),
 4.87 (1H,brs), 5.92 (1H,d,J=7.5Hz),
 7.03 (1H,d,J=7.5Hz), 7.32 (5H,m).

The following compound was also synthesized in a
 5 similar manner.



Referential Example 32:

1,4,5,6-Tetrahydro-6-ethyl-5-oxo-2-
piperazinopyrido[4,3-d]pyrimidine



Dissolved in 20 ml of ethanol was 1.0 g of the
 10 1,4,5,6-tetrahydro-6-ethyl-5-oxo-2-(4-benzylpiperazino)-
 pyrido[4,3-d]pyrimidine obtained in Referential Example
 31, followed by an addition of 10% Pd-C. The resultant
 mixture was stirred at 70°C for 2.5 hours in a
 hydrogen atmosphere. After removal of the catalyst by
 15 filtration, the filtrate was concentrated to obtain
 0.7 g of 1,4,5,6-Tetrahydro-6-ethyl-5-oxo-2-piperazino-
 pyrido[4,3-d]pyrimidine as crystals (yield: 95%).
 Melting point: 117 - 120°C (decomposed, deliquescent).

Mass spectrum: 247 (M^+).

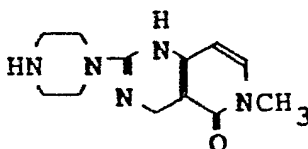
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.30 (3H,t,J=7Hz), 2.90 (4H,m), 3.55 (4H,m),

3.88 (2H,q,J=7Hz), 4.40 (2H,s),

5 5.98 (1H,d,J=7.5Hz), 7.03 (1H,d,J=7.5Hz).

The following compound was also synthesized in a similar manner.



Referential Example 33:

Ethyl 3-ethylaminopropionate



- 10 Dissolved in 500 ml of ethanol was 50 g (0.50 mol) of ethyl acrylate. While stirring the thus-prepared solution with ice cooling, a liquid mixture of 36 g (0.55 mol) of a 70% aqueous solution of ethylamine and 100 ml of ethanol was added dropwise over 3.5
- 15 hours. After allowing the reaction to proceed for further 3 hours, the solvents were distilled off. The residue was distilled under reduced pressure to obtain 50.5 g of the intended product as colorless liquid (yield: 70%).
- 20 Boiling point: 65°C/10 mmHg.
- Infrared absorption spectrum (neat, cm^{-1}):

3320 (broad), 1735.

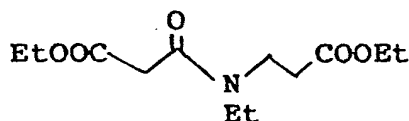
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.0 - 1.4 (6H,m), 2.4 - 3.0 (6H,m),

4.16 (2H,q,J=7.0Hz).

5 Referential Example 34:

Ethyl N-ethoxycarbonylacetyl-3-ethylamino-
propionate



While stirring with ice-cooling a mixture of
45 g (0.30 mol) of the ethyl 3-ethylaminopropionate
10 obtained in Referential Example 33, 37.3 g (0.27 mol)
of potassium carbonate, 250 ml of toluene and 250 ml
of water, 67.7 g (0.45 mol) of ethylmalonyl chloride
was dropped over 0.5 hour. After mixing the resultant
mixture at room temperature for further 3 hours, the
15 reaction mixture was allowed to separate into layers.
The toluene layer was washed successively with 5%
hydrochloric acid, saturated aqueous solution of sodium
bicarbonate, and saturated saline, and was then dried
with anhydrous magnesium sulfate. Toluene was
20 distilled off under reduced pressure to obtain 64.3 g
of the intended product as colorless liquid (yield:
83%).

Infrared absorption spectrum (neat, cm^{-1}):

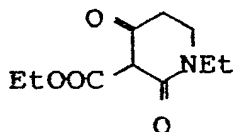
1735, 1648.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.1 - 1.3 (6H), 2.64 (2H), 3.2 - 3.8 (6H),
4.0 - 4.2 (4H).

Referential Example 35:

5 3-Carboethoxy-1-ethylpiperidine-2,4-dione



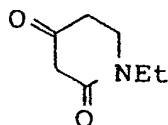
To an ethanol solution of sodium ethoxide which had been synthesized by adding 5.8 g of metallic sodium to 300 ml of ethanol, 62.2 g of ethyl N-ethoxycarbonylacetyl-3-ethylaminopropionate (Referential
10 Example 34) was added. The resultant mixture was refluxed for 4 hours. After allowing the reaction mixture to cool down, ethanol was distilled off. Ethyl acetate and a dilute aqueous solution of hydrogen chloride were added. The resulting mixture was shaken.
15 After washing the organic layer with water, it was dried and concentrated to obtain 36.3 g of 3-carboethoxy-1-ethylpiperidine-2,4-dione as an oily substance (yield: 71%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

20 1.28 (6H,m), 2.66 (2H,m), 3.44 (4H,m),
 4.32 (2H,m).

Referential Example 36:

1-Ethylpiperidine-2,4-dione



Added to 36.0 g of 3-carboethoxy-1-ethyl-
piperidine-2,4-dione (Referential Example 35) was
300 ml of a 10% aqueous solution of hydrochloric acid.

- 5 The resultant mixture was refluxed for 40 minutes.
After allowing the reaction mixture to cool down, it
was extracted with chloroform. The chloroform layer
was washed with water, dried and then concentrated,
thereby obtaining 16.6 g of 1-ethylpiperidine-2,4-dione
10 as a light yellowish oily substance (yield: 70%).

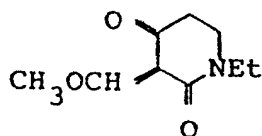
¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.20 (3H,t,J=7Hz), 2.64 (2H,t,J=7Hz),

3.36 (2H,s), 3.54 (4H,m).

Referential Example 37:

- 15 1-Ethyl-3-methoxymethylenepiperidine-2,4-dione



Added to 8.3 g of 1-ethylpiperidine-2,4-dione
were 11 g of methyl orthoformate and 20 ml of acetic
anhydride. The resultant mixture was refluxed for 7

hours. After allowing the reaction mixture to cool down, excess methyl orthoformate and acetic anhydride were distilled off under reduced pressure. The brown residue was distilled under reduced pressure in a

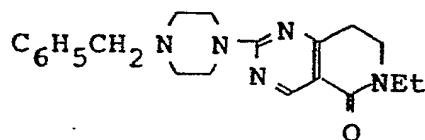
5 Kugelroll apparatus (0.5 mmHg; bath temperature: 200 - 250°C) to obtain 2.7 g of 1-ethyl-3-methoxymethylenepiperidine-2,4-dione as crystals (yield: 25%). The crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to obtain needles.

10 ¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.20 (3H,m), 2.64 (2H,t,J=7Hz), 3.50 (4H,m),
4.12 (3H,s), 7.86 (1H, two singlets).

Referential Example 38:

15 2-(4-Benzylpiperazino)-6-ethyl-5-oxo-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



To a suspension which had been obtained by adding 1.56 g of 1-amidino-4-benzylpiperazine sulfate to an ethanol solution of 0.23 g of sodium hydroxide, 1.07 g of 1-ethyl-3-methoxymethylenepiperidine-2,4-

20 dione (Referential Example 37) was added. The resultant mixture was refluxed for 2 hours. After distilling off ethanol, water was added to the residue,

followed by extraction with chloroform. After drying the chloroform layer, it was concentrated to obtain 1.4 g of 2-(4-benzylpiperazino)-6-ethyl-5-oxo-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (yield: 69%).

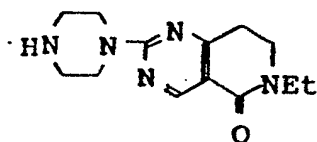
5 Melting point: 128 - 130°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.20 (3H,t,J=7Hz), 2.50 (4H,m),
2.94 (2H,t,J=8Hz), 3.55 (6H,m), 3.92 (4H,m),
7.32 (5H,m), 8.92 (1H,s).

10 Referential Example 39:

6-Ethyl-5-oxo-2-piperazino-5,6,7,8-tetra-
hydropyrido[4,3-d]pyrimidine



Dissolved in 20 ml of ethanol was 0.70 g of 2-(4-benzylpiperazino)-6-ethyl-5-oxo-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (Referential Example 38),
15 followed by an addition of 10% Pd-C. The resultant mixture was stirred at 60°C for 4 hours in a hydrogen atmosphere. After allowing the reaction mixture to cool down, the catalyst was filtered off and the
20 filtrate was concentrated to obtained 0.50 g of 6-ethyl-5-oxo-2-piperazino-5,6,7,8-tetrahydropyrido-

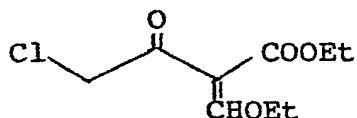
[4,3-d]pyrimidine as crystals (yield: 96%). The crystals were purified by their immersion in ethyl acetate.

Melting point: 205 - 210°C.

- 5 ^1H -NMR spectrum (CDCl_3 solution, δ ppm):
1.20 (3H,t,J=7Hz), 3.00 (6H,m), 3.60 (4H,m),
3.94 (4H,m), 8.84 (1H,s).

Referential Example 40:

Ethyl 4-chloro-2-ethoxymethyleneacetoacetate



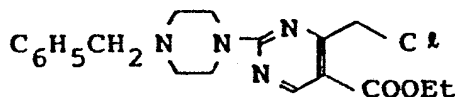
- 10 After heating and stirring 10 g (60.7 mmol) of ethyl 4-chloroacetoacetate, 18 g (121 mmol) of ethyl orthoformate and 25 g (245 mmol) of acetic anhydride at 110°C for 3 hours, excess ethyl orthoformate and acetic anhydride were distilled off under reduced
15 pressure and the residue was recrystallized from hexane to obtain 12.1 g of a solid substance as needles (yield: 90%).

Melting point: 86.5°C.

- ^1H -NMR spectrum (CDCl_3 solution, δ ppm):
20 1.35 (3H,t,J=7Hz), 1.44 (3H,t,J=7Hz),
4.30 (2H,q,J=7Hz), 4.33 (2H,q,J=7Hz),
4.56 (2H,s), 7.88 (1H,s).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

2900, 2830, 1686, 1670, 1575, 1250, 1018.

Referential Example 41:Ethyl 4-chloromethyl-2-(4-benzylpiperazino)-
pyrimidine-5-carboxylate

A solution, which had been prepared by
 5 dissolving 1.5 g of NaOH in 15 ml of H₂O, was added
 to a suspension of 9.7 g (36.4 mmol) of 1-amidino-4-
 benzylpiperazine sulfate and 185 ml of THF to
 neutralize the suspension.

Thereafter, a solution of 8 g (36.4 mmol) of the
 10 ethyl 4-chloro-2-ethoxymethyleneacetoacetate obtained
 in Referential Example 40 in 200 ml of THF was added
 dropwise at 20°C. After completion of the dropwise
 addition, 300 ml of ether was added. The resultant
 mixture was washed three times with water. After
 15 drying the organic layer with anhydrous MgSO₄, the
 solvent was distilled off under reduced pressure to
 obtain 11.8 g of the intended product with a light
 yellowish color (yield: 86.7%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

20 1.37 (3H,t,J=7Hz), 2.51 (4H,t,J=6Hz),
 3.75 (2H,s), 3.97 (4H,t,J=6Hz),
 4.34 (2H,q,J=7Hz), 4.88 (2H,s), 7.32 (5H,s),

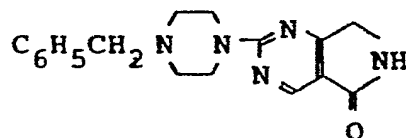
8.87 (1H,s).

Infrared absorption spectrum (neat, cm^{-1}):

2873, 2780, 1706, 1582, 1526, 1445, 1350,
1250, 1090, 1000, 742, 696.

5 Referential Example 42:

2-(4-Benzylpiperazino)-5-oxo-5,6-dihydro(7H)-
pyrrolo[3,4-d]pyrimidine



Dissolved in 10 ml of ethanol was 2.25 g (6 mmol) of ethyl 4-chloromethyl-2-(4-benzylpiperazino)-
10 pyrimidine-5-carboxylate (Referential Example 41),
followed by an addition of 10 ml (59 mmol) of a 30% aqueous NH_4OH solution at 20°C . The resultant mixture was stirred for 12 hours. The reaction mixture was poured in a 10% aqueous NaHCO_3 solution, followed
15 by extraction with CHCl_3 . The solvent was then distilled off and the residue was recrystallized from toluene.

Yield: 0.70 g (38%).

Melting point: 172°C .

20 ^1H -NMR spectrum ($\text{DMSO}-d_6$ solution, δ ppm):

2.45 (4H,t,J=6Hz), 3.50 (2H,s),

3.83 (4H,t,J=6Hz), 4.20 (2H,s), 7.30 (5H,s),

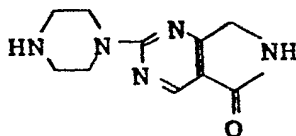
8.20 (1H,br.s), 8.57 (1H,s).

Infrared absorption spectrum (nujol, cm^{-1}):

2900, 1715, 1674, 1607, 1562, 1218, 1145,
730, 720.

5 Referential Example 43:

2-Piperazino-5-oxo-5,6-dihydro(7H)pyrrolo-
[3,4-d]pyrimidine



While heating at 60°C 1.6 g (5.18 mmol,
Referential Example 42) of 2-(4-benzylpiperazino)-5-
10 oxo-5,6-dihydro(7H)pyrrolo[3,4-d]pyrimidine, 0.16 g of
10% Pd-C and 30 ml of AcOH, H_2 was bubbled. One
hour later, Pd-C was filtered off and then the solvent
was distilled off. The residue was suspended in a 10%
aqueous NaHCO_3 solution.

15 Insoluble matter was collected by filtration.
Toluene was added to the solid and then toluene was
distilled off under reduced pressure to obtain 0.75 g
of the intended product (yield: 66%; oil).

^1H -NMR spectrum ($\text{DMSO}-d_6$ solution, δ ppm):

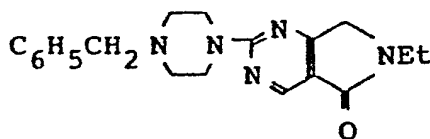
20 2.80 (4H,br.s), 3.24 (1H,br.s),
3.78 (4H,br.s), 4.23 (2H,s), 8.18 (1H,br.s),
8.58 (1H,s).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

3210, 3100, 2920, 2880, 1700, 1612, 1260,
1150, 980.

Referential Example 44:

5 6-Ethyl-2-(4-benzylpiperazino)-5-oxo-5,6-
 dihydro(7H)pyrrolo[3,4-d]pyrimidine



Dissolved in 10 ml of ethanol was 1.0 g (2.7
mmol, Referential Example 41) of ethyl 4-chloromethyl-
2-(4-benzylpiperazino)pyrimidine-5-carboxylate,
10 followed by an addition of 5 g (59 mmol) of a 70%
aqueous solution of ethylamine at 20°C. The resultant
mixture was stirred for 2 hours and was stirred for
further 0.5 hour at 80°C.

After completion of the reaction, the reaction
15 mixture was poured in water, neutralized with a 10%
aqueous NaHCO_3 solution, and then extracted with
ether. After drying the organic layer, the solvent was
distilled off and the residue was recrystallized from
toluene/hexane [yield: 0.82 g (91%)].

20 Melting point: 159.2°C.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.22 (3H, t, $J=7\text{Hz}$), 2.50 (4H, t, $J=6\text{Hz}$),

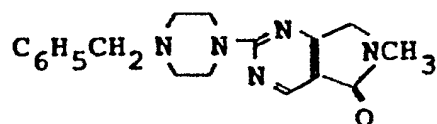
3.55 (2H,s), 3.59 (2H,q,J=7Hz),
3.93 (4H,t,J=6Hz), 4.18 (2H,s), 7.32 (5H,s),
8.64 (1H,s).

Infrared absorption spectrum (nujol, cm^{-1}):

5 2900, 1666, 1624, 1566, 1280, 1148, 1000,
 975, 795, 733.

Each of the following four compounds was also
obtained in a similar manner.

10 6-Methyl-2-(4-benzylpiperazino)-5-oxo-5,6-
 dihydro(7H)pyrrolo[3,4-d]pyrimidine



Yield: 94%.

Melting point: 178 - 179°C.

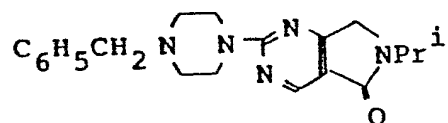
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

15 2.52 (4H,m), 3.15 (3H,s), 3.58 (2H,s),
 3.96 (4H,m), 4.20 (2H,s), 7.36 (5H,m),
 8.65 (1H,s).

Infrared absorption spectrum (CHCl_3 , cm^{-1}):

1685, 1618, 1522, 1350.

20 6-Isopropyl-2-(4-benzylpiperazino)-5-oxo-5,6-
 dihydro(7H)pyrrolo[3,4-d]pyrimidine



Yield: 39%.

Melting point: 173 - 174°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.25 (6H,d,J=7Hz), 2.52 (4H,m), 3.58 (2H,s),
 5 3.96 (4H,m), 4.16 (2H,s), 4.64 (1H,sept.,J=7Hz),
 7.36 (5H,m), 8.66 (1H,s).

Infrared absorption spectrum (CHCl₃, cm⁻¹):

1680, 1618, 1530, 1345.

6-n-Propyl-2-(4-benzylpiperazino)-5-oxo-5,6-
 10 dihydro(7H)pyrrolo[3,4-d]pyrimidine



Yield: 67%.

Melting point: 148 - 150°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

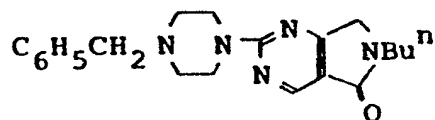
0.95 (3H,t,J=7Hz), 1.65 (2H,hextet,J=7Hz),
 15 2.52 (4H,m), 3.52 (2H,t,J=7Hz), 3.58 (2H,s),
 3.96 (4H,m), 4.21 (2H,s), 7.37 (5H,s),
 8.68 (1H,s).

Infrared absorption spectrum (CHCl₃, cm⁻¹):

- 79 -

3000, 1680, 1610, 1520, 1342, 1000.

6-n-Butyl-2-(4-benzylpiperazino)-5-oxo-5,6-
dihydro(7H)pyrrolo[3,4-d]pyrimidine



Yield: 62%.

5 Melting point: 144 - 146°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

0.96 (3H,t,J=7Hz), 1.16 - 1.80 (4H),
 2.52 (4H,m), 3.57 (2H,s), 3.57 (2H,t,J=7Hz),
 3.96 (4H,m), 4.20 (2H,s), 7.37 (5H,s),
 8.68 (1H,s).

10

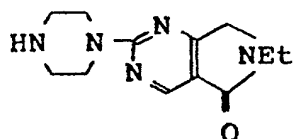
Infrared absorption spectrum (CHCl₃, cm⁻¹):

3010, 1680, 1610, 1520, 1342, 1000.

Referential Example 45:

6-Ethyl-2-piperazino-5-oxo-5,6-dihydro(7H)-
pyrrolo[3,4-d]pyrimidine

15



Added to 20 ml of AcOH were 1.5 g (4.45 mmol,
 Referential Example 44) of 6-ethyl-2-(4-benzyl-
 piperazino)-5-oxo-5,6-dihydro(7H)pyrrolo[3,4-d]-

pyrimidine and 0.15 g of 10% Pd-C. While bubbling H₂ at 80°C, the reaction was conducted for 1 hour.

After completion of the reaction, Pd-C was filtered off, AcOH was distilled off under reduced pressure, the residue was dissolved in chloroform, and the chloroform solution was neutralized with a 10% aqueous NaHCO₃ solution. Thereafter, the organic layer was dried with anhydrous MgSO₄, the solvent was distilled off, and the residue was purified by silica gel column chromatography [yield: 0.50 g (45%)].
Melting point: 58.5°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

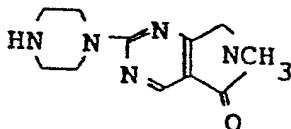
1.24 (3H, t, J=7Hz), 2.12 (1H, br.s),
2.95 (4H, br.s), 3.62 (2H, q, J=7Hz),
3.92 (4H, br.s), 4.21 (2H, s), 8.66 (1H, s).

Infrared absorption spectrum (KBr tablet, cm⁻¹):

3480, 3300, 2900, 1650, 1618, 1520, 1438,
1236, 1160, 862.

Each of the following four compounds was also obtained in a similar manner.

6-Methyl-2-piperazino-5-oxo-5,6-dihydro-
(7H)pyrrolo[3,4-d]pyrimidine



Yield: about 100%.

Melting point: 176 - 177°C.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

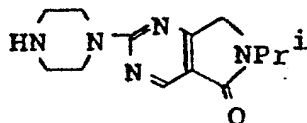
2.98 (4H,m), 3.18 (3H,s), 3.96 (4H,m),

5 4.24 (2H,s), 8.70 (1H,s).

Infrared absorption spectrum (CHCl_3 , cm^{-1}):

1685, 1618, 1522, 1350.

6-Isopropyl-2-piperazino-5-oxo-5,6-
dihydro(7H)pyrrolo[3,4-d]pyrimidine



10 Yield: 96%

Melting point: 161 - 162°C.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

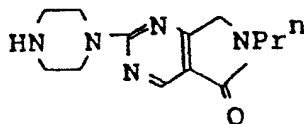
1.28 (6H,d,J=7Hz), 2.96 (4H,m), 3.94 (4H,m),

4.18 (2H,s), 4.65 (1H,sept.,J=7Hz), 8.70 (1H,s).

15 Infrared absorption spectrum (CHCl_3 , cm^{-1}):

1680, 1618, 1520, 1345.

6-n-Propyl-2-piperazino-5-oxo-5,6-
dihydro(7H)pyrrolo[3,4-d]pyrimidine



Yield: about 100%.

Melting point: 133 - 137°C.

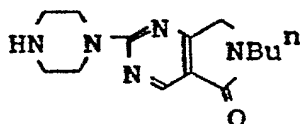
¹H-NMR spectrum (CDCl₃ solution, δ ppm):

0.96 (3H,t,J=7Hz), 1.66 (2H,hextet,J=7Hz),
 5 1.83 (1H,s), 2.96 (4H,m), 3.53 (2H,t,J=7Hz),
 3.93 (4H,m), 4.22 (2H,s), 8.70 (1H,s).

Infrared absorption spectrum (CHCl₃, cm⁻¹):

3400, 3340, 3000, 2970, 1680, 1610, 1570,
 1520, 1345, 1260.

10 6-n-Butyl-2-piperazino-5-oxo-5,6-
 dihydro(7H)pyrrolo[3,4-d]pyrimidine



Yield: about 100%.

Melting point: 108 - 112°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

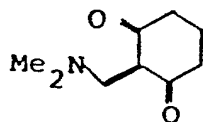
15 0.95 (3H,t,J=7Hz), 1.65 (2H,hextet,J=7Hz),
 2.52 (4H,m), 3.52 (2H,t,J=7Hz), 3.58 (2H,s),
 3.96 (4H,m), 4.21 (2H,s), 7.37 (5H,s),
 8.68 (1H,s).

Infrared absorption spectrum (CHCl₃, cm⁻¹):

20 3430, 3340, 3000, 2960, 2930, 1680, 1610,
 1575, 1520, 1455, 1435, 1350.

Referential Example 46:

2-Dimethylaminomethylenecyclohexane-1,3-dione



While stirring 5.60 g (50 mmol) of cyclohexane-1,3-dione under ice-cooling, 11.9 g (100 mmol) of N,N-dimethylformamidodimethylacetal was added dropwise. They were reacted at 25°C for further 7 hours. Low b.p. fractions were distilled off under reduced pressure from the reaction mixture. The residue was recrystallized from ethyl acetate-hexane to obtain 7.7 g of the intended product as yellowish crystals (yield: 92%).

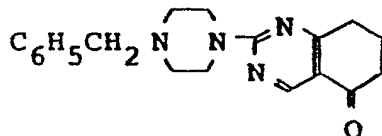
Melting point: 106 - 107°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.92 (2H,m), 2.47 (4H,m), 3.18 (3H,s),
3.40 (3H,s), 8.05 (1H,s).

Referential Example 47:

2-(4-Benzylpiperazino)-5-oxo-5,6,7,8-tetrahydroquinazoline



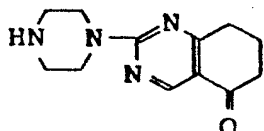
To an ethanol suspension (60 ml) of 10.73 g (40 mmol) of 1-amidino-4-benzylpiperazine sulfate, were added an ethanol solution (80 ml) of 1.6 g (40 mmol) of sodium hydroxide and then 6.69 g (40 mmol) of the
5 2-dimethylaminomethylenecyclohexane-1,3-dione obtained in Referential Example 46. The resultant mixture was heated under reflux for 4 hours. After cooling the reaction mixture to room temperature, the solvent was distilled off. The residue was added with 100 ml of
10 water and then extracted twice with 200 ml of ethyl acetate. The ethyl acetate layer was washed with saturated saline and then dried with anhydrous magnesium sulfate. Ethyl acetate was the distilled off under reduced pressure. The residue was purified by
15 silica gel column chromatography (eluent: ethyl acetate/hexane = 3/7) to obtain 9.90 g of the intended product as light yellowish crystals (yield: 77%).
Melting point: 96 - 97°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

20 1665, 1590, 1530, 1515.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

2.08 (2H,m), 2.5 (6H,m), 2.80 (2H,m),
3.54 (2H,s), 3.96 (4H,m), 7.32 (5H,s),
8.83 (1H,s).

Referential Example 48:2-Piperazino-5-oxo-5,6,7,8-
tetrahydroquinazoline

Dissolved in 30 ml of ethanol and 10 ml of
5 acetic acid was 0.64 g (2 mmol, Referential Example 47)
of 2-(4-benzylpiperazino)-5-oxo-5,6,7,8-tetrahydro-
quinazoline, followed by an addition of 64 mg of 10%
Pd-C. The quinazoline derivative was hydrogenated at
50°C for 1 hour under atmospheric pressure. After
10 cooling the reaction mixture to room temperature, the
catalyst was filtered off and the solvent was distilled
off from the filtrate under reduced pressure. The
residue was recrystallized from ethyl acetate to obtain
0.42 g of the intended product as light yellowish
15 crystals (yield: 90%).

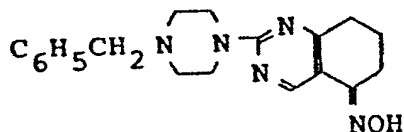
Melting point: 161 - 162°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

3400 (broad), 1670, 1600, 1530.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

20 2.10 (2H,m), 2.60 (2H,m), 2.84 (2H,m),
3.06 (4H,m), 4.08 (4H,m), 8.85 (1H,s).

Referential Example 49:2-(4-Benzylpiperazino)-5,6,7,8-tetrahydro-
5-hydroxyiminoquinazoline

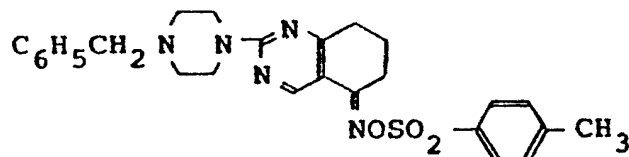
Added to 30 ml of methanol were 2.6 g (8.07
5 mmol, Referential Example 48) of 2-(4-benzyl-
piperazino)-5-oxo-5,6,7,8-tetrahydroquinazoline and
0.67 g (9.64 mmol) of hydroxylamine hydrochloride. The
resultant mixture was heated with stirring at 60°C for
2 hours. The reaction mixture was cooled to 20°C and
10 the resultant precipitate was collected by filtration,
thereby obtaining 2.85 g of white solid (yield: 95%).
Melting point: over 300°C (decomposed).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.80 (2H,m), 2.40 - 2.90 (8H,m), 3.58 (2H,s),
15 3.92 (4H,t,J=6Hz), 7.34 (5H,s), 8.91 (1H,s).

Infrared absorption spectrum (KBr tablet, cm⁻¹):

3150, 2920, 2444, 1618, 1582, 1510, 1500, 1275,
1032, 955.

Referential Example 50:2-(4-Benzylpiperazino)-5,6,7,8-tetrahydro-5-(p-toluenesulfonyl)iminoquinazoline

Added to a mixture of 30 ml of acetone, 2 g
 5 (5.35 mmol, Referential Example 49) of 2-(4-benzyl-
 piperazino)-5,6,7,8-tetrahydro-5-hydroxyiminoquina-
 zoline, and 1.6 g (8.4 mmol) of p-toluenesulfonyl
 chloride was a solution of 0.7 g (11 mmol) of KOH in 10
 ml of water. The resultant mixture was stirred at
 10 20°C for 4 hours.

After completion of the reaction, the reaction
 mixture was poured in saline and then extracted with
 ethyl acetate. The organic layer was dried to solid
 and the residue was purified by silica gel column
 15 chromatography (eluent: CHCl_3 -ethanol), thereby
 obtaining 1.5 g of white solid (yield: 59%).

Melting point: 180.6°C.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

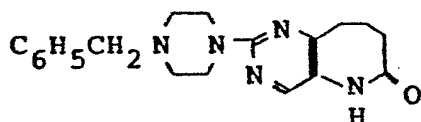
1.68 - 1.98 (2H,m), 2.44 (3H,s),
 20 2.46 - 2.85 (8H,m), 3.57 (2H,s),
 3.90 (4H,t,J=6Hz), 7.26 - 7.40 (7H,m),
 7.86 (1H,s), 7.95 (1H,s), 8.69 (1H,s).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

2920, 1578, 1526, 1424, 1188, 1176, 1005, 992.

Referential Example 51:

5 2-(4-Benzylpiperazino)-6-oxo-6,7,8,9-
 tetrahydro(5H)pyrimido[5,4-b]azepine



Dissolved in 30 ml of acetic acid was 1.3 g (4 mmol, Referential Example 50) of 2-(4-benzylpiperazino)-5,6,7,8-tetrahydro-5-(p-toluenesulfonyl)iminoquinazoline). The resultant mixture was heated at 100°C for 4 hours. After completion of the reaction, acetic acid was distilled off. The residue was dissolved in CHCl_3 . After neutralizing and washing the thus-obtained chloroform solution with a 10% aqueous NaHCO_3 solution, the solvents were distilled off and the residue was recrystallized from toluene to obtain 0.70 g of white solid (yield: 97%).

Melting point: 210.7°C.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

2.26 - 2.40 (4H,m), 2.49 (4H,t,J=6Hz),
 2.83 (2H,t,J=7Hz), 3.55 (2H,s),
 3.82 (4H,t,J=6Hz), 7.32 (5H,s),
 7.83 (1H,s), 7.94 (1H,s).

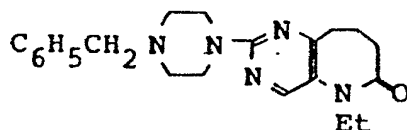
Infrared absorption spectrum (KBr tablet, cm^{-1}):

3150, 2900, 2830, 1660, 1595, 1346, 1010, 982.

Referential Example 52:

5-Ethyl-2-(4-benzylpiperazino)-6-oxo-

5 6,7,8,9-tetrahydro(5H)pyrimido[5,4-b]azepine



Added to 30 ml of THF were 0.65 g (1.84 mmol, Referential Example 51) of 2-(4-benzylpiperazino)-6-oxo-6,7,8,9-tetrahydro(5H)pyrimido[5,4-b]azepine and 0.15 g (3.75 mmol) of 60% NaH. The resultant mixture was stirred at 20°C for 30 minutes. Thereafter, 3 g (27.8 mmol) of ethyl bromide was added and the reaction mixture was heated to 60°C at which the reaction was conducted for 5 hours. After completion of the reaction, the solvent was distilled off and the residue was purified by silica gel column chromatography to obtain 0.65 g of a colorless oil (yield: 92%).

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.15 (3H,t,J=7Hz), 2.16 - 2.38 (4H,m),

2.53 (4H,t,J=6Hz), 2.74 (2H,t,J=5.5Hz),

20 2.58 (2H,s), 3.80 (2H,q,J=7Hz),

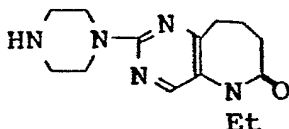
3.87 (4H,t,J=6Hz), 7.35 (5H,s), 8.13 (1H,s).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

2920, 1657, 1589, 1444, 1250, 1000, 980.

Referential Example 53:

5-Ethyl-2-piperazino-6-oxo-6,7,8,9-
tetrahydro(5H)pyrimido[5,4-b]azepine



5 To a mixed solvent of 30 ml of acetic acid and
10 ml of ethanol, 0.6 g (2.18 mmol, Referential
Example 52) of 5-ethyl-2-(4-benzylpiperazino)-6-oxo-
6,7,8,9-tetrahydro(5H)pyrimido[5,4-b]azepine and 0.06 g
of 10% Pd-C were added. While causing hydrogen gas to
10 flow through the reaction mixture, the reaction was
allowed to proceed at 100°C for 4 hours. Thereafter,
the Pd/C was filtered off and the filtrate was dried to
obtain 0.5 g of a light yellowish oily substance
(yield: about 100%).

15 ¹H-NMR spectrum (CDCl₃ solution, δ ppm):

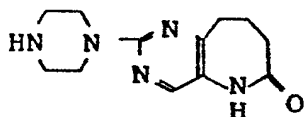
1.16 (3H,t,J=7Hz), 2.21 - 2.40 (4H,m),
2.75 (2H,t,J=5.5Hz), 2.96 (4H,t,J=6Hz),
3.70 - 4.05 (6H,m), 8.15 (1H,s).

Infrared absorption spectrum (neat, cm⁻¹):

20 3460, 3300, 2940, 1650, 1595, 1445, 1128, 984.

Similarly, the following compound was also
obtained by the following procedure.

2-Piperazino-6-oxo-6,7,8,9-tetrahydro(5H)pyrimido-
[5,4-b]azepine



Added to 20 ml of ethanol were 0.1 g (0.3 mmol, Referential Example 51) of 2-(4-benzylpiperazino)-6-oxo-6,7,8,9-tetrahydro(5H)pyrimido[5,4-b]azepine and 0.01 g of 10% Pd-C. In a hydrogen atmosphere, they were reacted at 50°C for 4 hours. After filtering off the Pd-C, the filtrate was dried to solid to obtain 0.074 g of colorless crystals in a quantitative yield.

Melting point: 175 - 178°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

2.2-2.5 (4H,m), 2.7-3.0 (2H,m),

2.94 (4H,t,J=4.5Hz), 3.81 (4H,t,J=4.5Hz),

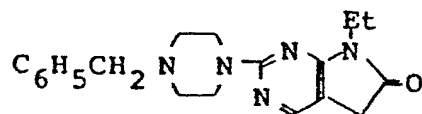
7.00 (1H,br.s), 7.98 (1H,s).

Infrared absorption spectrum (nujol, cm⁻¹):

1685, 1600, 1505, 1350, 1255.

Referential Example 54

2-(4-Benzylpiperazino)-5,6-dihydro-7-ethyl-
6-oxo(7H)pyrrolo[2,3-d]pyrimidine



A mixture of 1.41 g (3.76 mmol, Referential Example 71) of ethyl 2-(4-benzylpiperazino)-4-chloropyrimidine-5-acetate, 5 ml of ethylamine and 20 ml of isopropanol was placed in a pressure vessel, in which they were heated at 120°C for 2 hours. The solvent was then driven off under reduced pressure. The residue was added with water, followed by extraction with chloroform. After drying the organic layer with MgSO_4 , it was concentrated. The residue was purified by silica gel column chromatography to obtain 0.58 of the above-identified compound (yield: 46%).

Melting point: 110 - 113°C.

Infrared absorption spectrum (CDCl_3 solution, cm^{-1}):

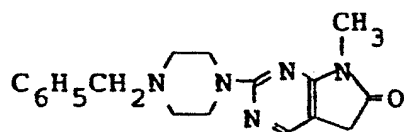
1725, 1620, 1570.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.25 (3H,t,J=7.0Hz), 2.49 (4H,t,J=5.2Hz),
3.37 (2H,s), 3.54 (2H,s), 3.75 (2H,q,J=7.2Hz),
3.83 (4H,t,J=5.2Hz), 7.31 (5H,s), 7.89 (1H,s).

Similarly, the following two compounds were also obtained.

2-(4-Benzylpiperazino)-5,6-dihydro-7-methyl-6-oxo(7H)-pyrrolo[2,3-d]pyrimidine



Yield: 72%.

Melting point: 172 - 174°C.

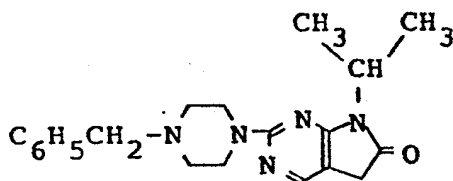
5 ¹H-NMR spectrum (CDCl₃ solution, δ ppm):

2.50 (4H,m), 3.18 (3H,s), 3.40 (2H,s),
3.54 (2H,s), 3.84 (4H,m), 7.34 (5H,m),
7.90 (1H,s).

Infrared absorption spectrum (KBr tablet, cm⁻¹):

10 1735, 1630, 1575, 1520, 1480, 1340, 1245.

2-(4-Benzylpiperazino)-5,6-dihydro-7-isopropyl-6-oxo(7H)pyrrolo[2,3-d]pyrimidine



Yield: 36%.

Melting point: 125 - 127°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

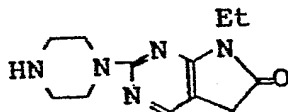
1.48 (6H,d,J=7Hz), 2.50 (4H,m), 3.36 (2H,s),
3.56 (2H,s), 3.82 (4H,m), 4.62 (1H,sept.,J=7Hz),
7.33 (5H,m), 7.89 (1H,s).

5 Infrared absorption spectrum (KBr tablet, cm⁻¹):

1730, 1620, 1580, 1440, 1220, 1100.

Referential Example 55:

5,6-Dihydro-7-ethyl-6-oxo-2-piperazino(7H)-
pyrrolo[2,3-d]pyrimidine



- 10 Using as a solvent 15 ml of ethanol which
contained 0.12 ml of formic acid, 0.54 g (1.60 mmol,
Referential Example 54) of 2-(4-benzylpiperazino)-5,6-
dihydro-7-ethyl-6-oxo(7H)pyrrolo[2,3-d]pyrimidine was
hydrogenated at normal pressure in the presence of 0.1
15 g of 10% Pd-C. After being refluxed for 4.5 hours, the
catalyst was filtered off and ethanol was distilled off
under reduced pressure. The residue was added with an
aqueous solution of sodium carbonate, followed by
extraction with chloroform. The organic layer was
20 dried with MgSO₄ and then concentrated, thereby
obtaining 0.36 g of the above-identified compound as an
oily product (yield: 91%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

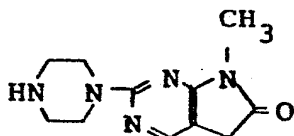
1.27 (3H,t,J=7.0Hz), 2.02 (1H,br.s),

2.92 (4H,t,J=5.2Hz), 3.40 (2H,s),

3.80 (6H,m), 7.91 (1H,s).

5 The following compounds were also obtained in a similar manner.

5,6-Dihydro-7-methyl-6-oxo-2-piperazino(7H)pyrrolo-
[2,3-d]pyrimidine



Yield: 70%.

10 Melting point: 145 - 147°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

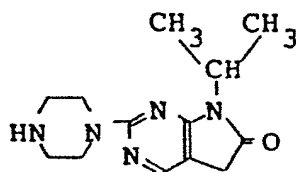
1.86 (1H,br.s), 2.94 (4H,m), 3.21 (3H,s),

3.43 (2H,s), 3.82 (4H,m), 7.93 (1H,s).

Infrared absorption spectrum (KBr tablet, cm⁻¹):

15 3340, 1738, 1630, 1580, 1450, 1105.

5,6-Dihydro-7-isopropyl-6-oxo-2-piperazino(7H)pyrrolo-
[2,3-d]pyrimidine



Yield: 83%.

Melting point: 113 - 115°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

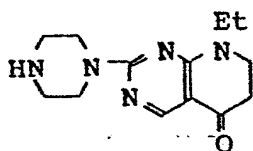
1.52 (6H,d,J=7Hz), 2.08 (1H, br.s), 2.93 (4H,m),
 3.40 (2H,s), 3.80 (4H,m), 4.65 (1H,sept.,J=7Hz),
 7.47 (1H,s), 7.93 (1H,s).

Infrared absorption spectrum (neat, cm⁻¹):

3330, 1725, 1622, 1575, 1440, 1220, 1110.

Referential Example 56:

8-Ethyl-5-oxo-2-piperazino-5,6,7,8-
tetrahydropyrido[2,3-d]pyrimidine



A mixture, which consisted of 2.5 g (11.3 mmol) of 8-ethyl-5-oxo-2-methylthio-5,6,7,8-tetrahydropyrido-[2,3-d]pyrimidine (synthesized by the process described in Japanese Patent Laid-Open No. 18600/1978), 2.93 g (34.0 mmol) of anhydrous piperazine and 20 ml of dimethylsulfoxide, was heated at 120°C for 3.5 hours

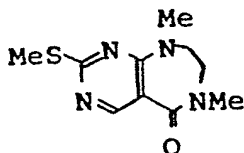
and then at 140°C for 6.5 hours. Dimethylsulfoxide was distilled off under reduced pressure. The residue was added with water, followed by extraction with chloroform. The organic layer was dried with MgSO_4 and then concentrated to obtain 3.08 g of the above-

¹H-NMR spectrum (CDCl_3 solution, δ ppm):

1.20 (3H,t,J=7.2Hz), 1.77 (1H,s),
2.61 (2H,dd,J=6.6,6.7Hz), 2.90 (4H,m),
3.59 (4H,m), 3.88 (4H,m), 8.59 (1H,s).

Referential Example 57:

6,9-Dimethyl-2-methylthio-5-oxo-5,6,7,8-tetrahydro(9H)pyrimido[4,5-e]diazepine



To a mixture of 4.58 ml (43.0 mmol) of N,N'-dimethylethylenediamine [synthesized by the process described in J. Am. Chem. Soc., 65, 350(1943)], 150 ml of EtOH and 2.51 g of Na_2CO_3 , an ethanol solution (50 ml) of 5.0 g (21.5 mmol) of ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate was added dropwise over 50 minutes. After being refluxed for 13 hours, ethanol was distilled off under reduced pressure. The residue was added with water, followed

by extraction with chloroform. The organic layer was dried and then concentrated. The residue was purified by silica gel column chromatography to obtain 3.55 g of the above-identified compound (yield: 69%).

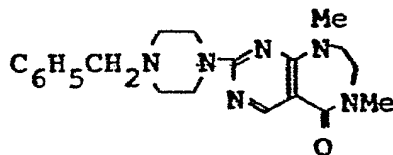
5 Melting point: 153 - 155°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

2.52 (3H,s), 3.13 (3H,s), 3.23 (3H,s),
3.63 (4H,ABqualt.), 8.72 (1H,s).

Referential Example 58:

10 6,9-Dimethyl-2-(4-benzylpiperazino)-5-oxo-
5,6,7,8-tetrahydro(9H)pyrimido[4,5-e]diazepine



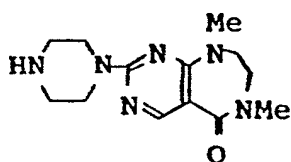
Continuously stirred at 140 - 170°C for 28 hours were 1.3 g (5.46 mmol) of 6,9-dimethyl-2-methylthio-5-oxo-5,6,7,8-tetrahydro(9H)pyrimido[4,5-e]-
15 diazepine and 4 g (22.69 mmol) of 1-benzylpiperazine. After cooling the reaction mixture, ethyl acetate was added to the reaction mixture and insoluble matter was filtered off. Then, the ethyl acetate solution was concentrated and the residue was purified by column
20 chromatography to obtain 0.2 g of the intended product as reddish brown oil (yield: 10%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

2.47 (4H,m), 3.11 (3H,s), 3.12 (3H,s),
3.55 (6H,m), 3.84 (4H,m), 7.32 (5H,m),
8.72 (1H,s).

Referential Example 59:

5 6,9-Dimethyl-2-piperazino-5-oxo-5,6,7,8-
 tetrahydro(9H)pyrimido[4,5-e]diazepine



Dissolved in 10 ml of ethanol was 0.2 g (0.55 mmol) of 6,9-dimethyl-2-(4-benzylpiperazino)-5-oxo-5,6,7,8-tetrahydro(9H)pyrimido[4,5-e]diazepine,
10 followed by an addition of 20 mg of 10% Pd-C. Under reflux, the reactant was hydrogenated at atmospheric pressure for 2 hours. After cooling the reaction mixture to room temperature, the catalyst was filtered off and the filtrate was concentrated under reduced
15 pressure. The residue was purified by column chromatography to obtain 0.1 g of the intended product (yield: 67%).

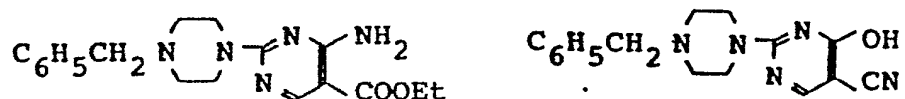
¹H-NMR spectrum (CDCl₃ solution, δ ppm):

3.59 (6H,s), 3.27 (4H,m), 3.62 (4H,br.s),
20 4.20 (4H,m), 8.70 (1H,s).

Referential Example 60:

Ethyl 4-amino-2-(4-benzylpiperazino)-
pyrimidine-5-carboxylate and 2-(4-
benzylpiperazino)-5-cyano-4-hydroxy-
pyrimidine

5



Mixed were 26.8 g of 1-amidino-4-benzyl-
 piperazine sulfate and 133 ml of a 3% ethanol solution
 of sodium hydroxide, followed by an addition of 17.0 g
 of ethyl 2-cyano-3-ethoxyacrylate. After being
 10 refluxed for 5 hours, the reaction mixture was allowed
 to cool down. After distilling off ethanol from the
 reaction mixture, the residue was added with water and
 ethyl acetate. The resultant mixture was shaken.
 Precipitated colorless crystals of 2-(4-benzyl-
 15 piperazino)-5-cyano-4-hydroxypyrimidine were collected
 by filtration, washed with water and then dried,
 thereby obtaining 7.4 g of 2-(4-benzylpiperazino)-5-
 cyano-4-hydroxypyrimidine (yield: 25%).

Melting point: 243 - 244°C.

20 ¹H-NMR spectrum (CDCl₃ solution, δ ppm):

2.45 (4H,m), 3.45 (2H,m), 3.50 (2H,s),
 3.73 (2H,m), 7.32 (5H,m), 8.12 (1H,s).

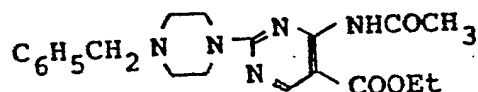
The filtrate was shaken, and the organic layer was dried and concentrated to obtain solid matter. The solid matter was added with ether. After removing insoluble matter, ether was distilled off to obtain 11.2 g of ethyl 4-amino-2-(4-benzylpiperazino)-pyrimidine-5-carboxylate as light yellowish crystals. Melting point: 224 - 245°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.34 (3H,t,J=7Hz), 2.46 (4H,m), 3.53 (2H,s),
3.86 (4H,m), 4.27 (2H,q,J=7Hz), 7.32 (5H,m),
8.63 (1H,s).

Referential Example 61:

Ethyl 4-acetylamino-2-(4-benzylpiperazino)-pyrimidine-5-carboxylate



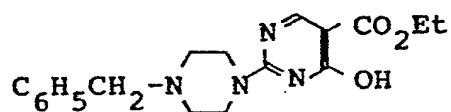
In acetic anhydride, 1.00 g of ethyl 4-amino-2-(4-benzylpiperazino)pyrimidine-5-carboxylate (the compound synthesized in Referential Example 60) was refluxed for 1 hour. After allowing the reaction mixture to cool down, acetic anhydride was distilled off and the resulting viscous oil was purified by silica gel column chromatography to obtain 0.68 g of the above-identified compound (yield: 61%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.36 (3H,t,J=7Hz), 2.48 (3H,s), 2.52 (4H,m),
3.56 (2H,s), 3.92 (4H,m), 4.33 (2H,q,J=7Hz),
7.33 (5H,m), 8.78 (1H,s).

5 Referential Example 62:

Ethyl 2-(4-benzylpiperazino)-4-hydroxy-
pyrimidine-5-carboxylate

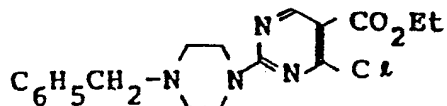


An ethanol solution of 25.2 g of sodium
hydroxide was added with 160 g (0.60 mol) of 1-amidino-
10 4-benzylpiperazine sulfate, followed by a dropwise
addition of 129.4 g (0.60 mol) of diethyl ethoxy-
methylenemalonate over 20 minutes. After being
refluxed for 5.5 hours, the reaction mixture was cooled
and the precipitated crystals were collected by
15 filtration. The thus-obtained crystals were washed
with water and then dried, thereby obtaining 131.4 g of
the above-identified compound (yield: 64%).

Melting point: 151 - 153°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

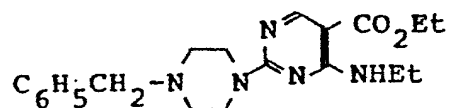
20 1.36 (3H,t,J=7Hz), 2.49 (4H,m), 3.54 (2H,s),
3.93 (4H,m), 4.35 (2H,q,J=7Hz), 7.31 (5H,s),
8.63 (1H,s).

Referential Example 63:Ethyl 2-(4-benzylpiperazino)-4-chloro-
pyrimidine-5-carboxylate

A mixture of 130.0 g (0.38 mol) of ethyl 2-(4-benzylpiperazino)-4-hydroxypyrimidine-5-carboxylate (the compound synthesized in Referential Example 62) and 390 ml of thionyl chloride was refluxed for 10 hours. After adding 600 ml of toluene, the resultant mixture was distilled to remove excess thionyl chloride. The reaction mixture was ice-cooled and was then added with an aqueous solution of sodium hydroxide to render it alkaline. It was then extracted with chloroform. After drying the chloroform layer with MgSO_4 , chloroform was distilled off under reduced pressure to obtain 120.2 g of the above-identified compound as an oily product (yield: 88%).

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.36 (3H, s, J=7Hz), 2.50 (4H, m), 3.56 (2H, br. s),
3.92 (4H, m), 4.32 (2H, q, J=7Hz), 7.35 (5H, s),
8.79 (1H, s).

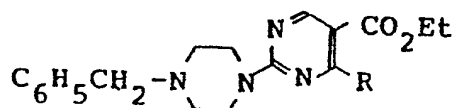
Referential Example 64:Ethyl 2-(4-benzylpiperazino)-4-ethylamino-
pyrimidine-5-carboxylate

To a mixture of 101.3 g (0.28 mol) of ethyl
5 2-(4-benzylpiperazino)-4-chloropyrimidine-5-carboxylate
(the compound synthesized in Referential Example 63)
and 590 ml of chloroform, 72.3 g (1.12 mol) of a 70%
aqueous solution of ethylamine was added dropwise over
15 minutes. The resultant mixture was stirred at room
10 temperature for 2 hours. The reaction mixture was
added with water, followed by extraction with
chloroform. After drying the chloroform layer with
MgSO₄, chloroform was distilled off to obtain 103.5 g
of the above-identified compound as an oily product
15 (yield: about 100%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.22 (3H,t,J=7Hz), 1.32 (3H,t,J=7Hz),
2.47 (4H,m), 3.46 (2H,d,q,J=5,7Hz), 3.54 (2H,s),
3.88 (4H,m), 4.25 (2H,q,J=7Hz), 7.31 (5H,s),
20 8.00 (1H,br.t,J=5Hz), 8.58 (1H,s).

Each of the following compounds was also
prepared in a similar manner.

R

NHCH₃ (m.p. 71 - 74°C) (synthesized from the compound of Ref. Ex. 63)

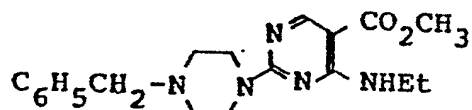
NHPrⁱ ditto

N(CH₃)₂ ditto

5 NEt₂ ditto

Referential Example 65:

Methyl 2-(4-benzylpiperazino)-4-ethylaminopyrimidine-5-carboxylate



10 To a methanol solution (10 ml) containing 0.24 g (4.44 mmol) of sodium methoxide, was added a methanol solution (10 ml) of 0.80 g (2.17 mmol) of ethyl 2-(4-benzylpiperazino)-4-ethylaminopyrimidine-5-carboxylate (the compound synthesized in Referential Example 64).

The resultant mixture was refluxed for 2 hours.

15 Methanol was distilled off under reduced pressure.

Water was added to the residue, followed by extraction with ethyl acetate. The organic layer was dried with MgSO₄ and ethyl acetate was distilled off under

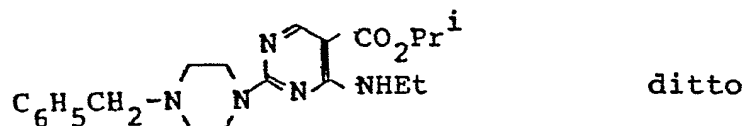
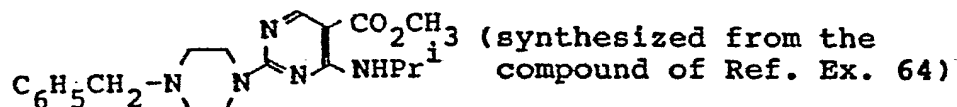
reduced pressure, thereby obtaining 0.75 g of the above-identified compound as an oily product (yield: 97%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

- 5 1.22 (3H,t,J=7Hz), 2.48 (4H,m),
 3.47 (2H,d,q,J=5,7Hz), 3.54 (2H,s),
 3.79 (3H,s), 3.83 (4H,m), 7.31 (5H,s),
 7.96 (1H,br.t,J=5Hz), 8.56 (1H,s).

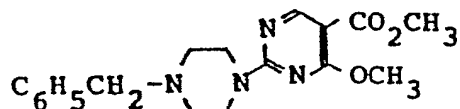
10 The following compounds were also synthesized in a similar manner.

Structural formula



Referential Example 66:

- 15 Methyl 2-(4-benzylpiperazino)-4-methoxypyrimidine-5-carboxylate



To a methanol solution (50 ml) of 1.88 g (34.8 mmol) of sodium methoxide, a methanol solution (40 ml) of 10.1 g (28.0 mmol) of ethyl 2-(4-benzylpiperazino)-4-chloropyrimidine-5-carboxylate (the compound
5 synthesized in Referential Example 63) was added dropwise over 10 minutes. The resultant mixture was stirred at room temperature for 1 hour. Methanol was distilled off under reduced pressure and water was added, followed by extraction with chloroform. After
10 drying the chloroform layer with MgSO_4 , chloroform was distilled off under reduced pressure and the residue was recrystallized from methanol-ethyl acetate to obtain 7.9 g of the above-identified compound (yield: 79%).

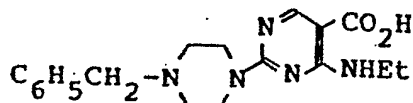
15 Melting point: 135 - 138°C.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

2.49 (4H,m), 3.54 (2H,s), 3.82 (3H,s),
3.90 (4H,m), 3.97 (3H,s), 7.32 (5H,s),
8.71 (1H,m).

20 Referential Example 67:

2-(4-Benzylpiperazino)-4-ethylamino-
pyrimidine-5-carboxylic acid



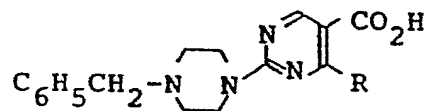
After refluxing for 1 hour a mixture of 106.4 g (0.29 mol) of ethyl 2-(4-benzylpiperazino)-4-ethyl-aminopyrimidine-5-carboxylate (the compound synthesized in Referential Example 64), 38.0 g (0.58 mol) of a 85% aqueous solution of potassium hydroxide, 100 ml of water and 400 ml of ethanol, ethanol was distilled off under reduced pressure. The residue was added with water and then neutralized with hydrochloric acid. The precipitated crystals were collected by filtration and were then dried to obtain 80.3 g of the above-identified compound (yield: 82%).

Melting point: 158 - 160°C.

¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

1.18 (3H,t,J=7Hz), 2.66 (4H,m),
 3.44 (2H,d,q,J=5,7Hz), 3.75 (2H,s),
 3.91 (4H,m), 7.35 (5H,s), 8.19 (1H,br.t,J=5Hz),
 8.45 (1H,s).

Each of the following compounds was also synthesized in a similar manner.

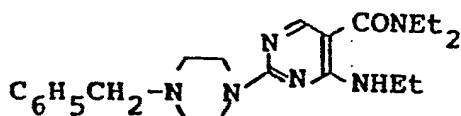


<u>R</u>	<u>m.p.</u>	
NH ₂	158 - 160°C	(synthesized from the compound of Ref. Ex. 60)
NHCH ₃	184 - 186°C	(synthesized from the compound of Ref. Ex. 64)

<u>R</u>	<u>m.p.</u>	
NHPr ⁱ		(synthesized from the ditto)
OCH ₃	208 - 210°C	(synthesized from the compound of Ref. Ex. 66)
SCH ₃		(synthesized from the compound of Ref. Ex. 76)

5 Referential Example 68:

2-(4-Benzylpiperazino)-4-ethylaminopyrimidine-
5-carboxylic acid diethylamide



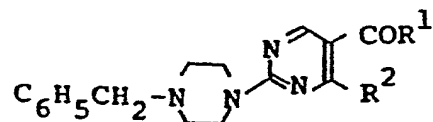
A mixture of 0.5 g (1.46 mmol) of 2-(4-benzyl-
 piperazino)-4-ethylaminopyrimidine-5-carboxylic acid
 10 (the compound synthesized in Referential Example 67)
 and 20 ml of chloroform was added with 0.2 ml (1.43
 mmol) of triethylamine, followed by a further addition
 of 0.22 ml (3.02 mmol) of thionyl chloride. The
 resultant mixture was stirred at room temperature for 1
 15 hour. After adding 1.0 ml (9.67 mmol) of diethylamine
 and stirring the resultant mixture for 1 hour, water
 was added. The resultant mixture was extracted with
 chloroform. After drying the chloroform layer with
 MgSO₄, the solvent was distilled off under reduced
 20 pressure and the residue was purified by silica gel
 column chromatography to obtain 0.37 g of the above-

identified compound (yield: 64%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.20 (3H,t,J=7Hz), 1.21 (3H,t,J=7Hz),
 1.25 (3H,t,J=7Hz), 2.48 (4H,m), 3.45 (6H),
 3.54 (2H,s), 3.84 (4H,m), 6.98 (1H,br.t,J=5Hz),
 7.32 (5H,s), 7.90 (1H,s).

Each of the following compounds was also
 synthesized in a similar manner.

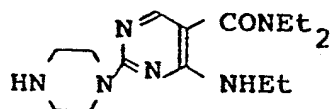


	<u>R¹</u>	<u>R²</u>	<u>m.p.</u>	<u>Ref. Ex. No. of corres. starting compound</u>
10	NHCH ₃	NHCH ₃		67
	NH ₂ t	NH ₂	163 - 164°C	67
	NH ₂ T	NH ₂ T		67
	N(CH ₃) ₂	NHCH ₃		67
	N(CH ₃) ₂	NH ₂ t		67
15	NEt ₂	NH ₂	116 - 120°C	67
	NEt ₂	NHCH ₃		67
	NEt ₂	NHPr ⁱ		67
	NEt ₂	OCH ₃		67
	NEt ₂	SCH ₃		67

\underline{R}^1	\underline{R}^2	<u>m.p.</u>	<u>Ref. Ex. No. of corres. starting compound</u>
NPr_2^{n}	NHET		67

Referential Example 69:

5 2-Piperazino-4-ethylaminopyrimidine-5-
carboxylic acid diethylamide

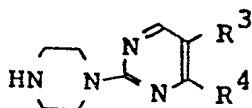


Using 20 ml of ethanol and 0.1 ml of 99% formic acid as solvents and 0.1 g of 10% Pd-C as a catalyst, 0.33 g (0.83 mmol) of 2-(4-benzylpiperazino)-4-ethylaminopyrimidine-5-carboxylic acid diethylamide (the compound synthesized in Referential Example 68) was refluxed for 1 hour for its hydrodecomposition. The catalyst was filtered off and the solvents were distilled off under reduced pressure, thereby obtaining 0.26 g of the above-identified compound as an oily product (yield: about 100%).

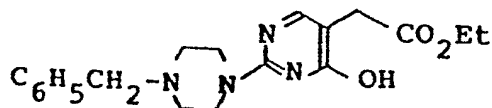
¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.23 (9H), 3.36 (4H,m), 4.47 (6H), 4.21 (4H,m),
 7.05 (1H,br.t,J=5Hz), 7.27 (5H,s), 7.90 (1H,s).

Each of the following compounds was also
 20 obtained in a similar manner.



	<u>R³</u>	<u>R⁴</u>	<u>m.p.</u>	<u>Ref. Ex. No. of corres. starting compound</u>
	CO ₂ CH ₃	NHEt	190 - 192°C	65
	CO ₂ CH ₃	NHPr ⁱ		65
	CO ₂ Et	OH	221 - 223°C	62
5	CO ₂ Et	NH ₂	208 - 210°C	60
	CO ₂ Et	NHCH ₃		64
	CO ₂ Et	N(CH ₃) ₂		64
	CO ₂ Et	NHEt		64
	CO ₂ Et	NEt ₂		64
10	CO ₂ Et	NHPr ¹		64
	CO ₂ Et	NHCOCH ₃	232 - 233°C	61
	CO ₂ Pr ⁱ	NHEt		65
	CONHCH ₃	NHCH ₃		68
	CONHEt	NH ₂		68
15	CONHEt	NHEt		68
	CON(CH ₃) ₂	NHCH ₃		68
	CON(CH ₃) ₂	NHEt		68
	CONEt ₂	NH ₂	248 - 250°C	68
	CONEt ₂	NHCH ₃		68
20	CONEt ₂	NHPr ⁱ		68
	CONEt ₂	OCH ₃		68
	CONEt ₂	SCH ₃		68
	CONPr ₂ ⁿ	NHEt		68
	CN	OH		60
25	CH ₂ CONHEt	NHEt		72

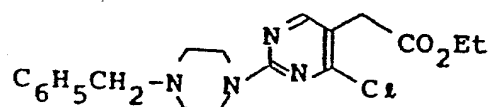
Referential Example 70:Ethyl 2-(4-benzylpiperazino)-4-hydroxy-
pyrimidine-5-acetate

Added to an ethanol solution of sodium ethoxide,
5 which had been prepared from 0.57 g (24.8 mmol) of
sodium and 30 ml of EtOH, was 6.61 g (24.7 mmol) of
1-amidino-4-benzylpiperazine sulfate, followed by a
dropwise addition of an ethanol solution (10 ml) of
5.0 g (24.7 mmol) of ethyl 2-formylsuccinate [the
10 compound described in Ann. 363, 340] over 15 minutes.
The resultant mixture was then refluxed for 4.5 hours.
After cooling the reaction mixture, crystals were
collected by filtration and then washed with water to
obtain 3.65 g of the above-identified compound (yield:
15 41%).

Melting point: 203 - 205°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

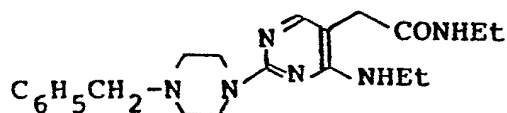
1.17 (3H,t,J=7Hz), 2.50 (4H,m), 3.26 (2H,s),
3.54 (2H,s), 3.71 (4H,m), 4.01 (2H,q,J=7Hz),
20 7.31 (5H,s), 7.66 (1H,s).

Referential Example 71:Ethyl 2-(4-benzylpiperazino)-4-chloro-
pyrimidine-5-acetate

A mixture of 3.0 g (8.00 mmol) of ethyl 2-(4-
5 benzylpiperazino)-4-hydroxypyrimidine-5-acetate (the
compound synthesized in Referential Example 70) and 50
ml of toluene was added with 1.12 ml (8.03 mmol) of
triethylamine and 0.90 ml (9.66 mmol) of phosphorus
oxychloride. The resultant mixture was stirred at room
10 temperature for 2 hours and was then refluxed for 1
hour. The mixture was poured in water, followed by
extraction with chloroform. The chloroform layer was
dried with MgSO_4 and the solvent was distilled off
under reduced pressure. The residue was purified by
15 alumina column chromatography to obtain 1.85 g of the
above-identified compound as an oily product (yield:
59%).

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.25 (3H,t,J=7Hz), 2.48 (4H,m), 3.53 (4H,s),
20 3.81 (4H,m), 4.17 (2H,q,J=7Hz), 7.31 (5H,s),
8.10 (1H,s).

Referential Example 72:2-(4-Benzylpiperazino)-4-ethylamino-
pyrimidine-5-acetic acid ethylamide

A mixture of 1.41 g (3.76 mmol) of ethyl 2-(4-
5 benzylpiperazino)-4-chloropyrimidine-5-acetate [the
compound synthesized in Referential Example 71], 5 ml
of ethylamine and 20 ml of isopropanol was placed in a
pressure vessel and was then heated at 120°C for 2
hours. Thereafter, the solvent was driven off under
10 reduced pressure and water was added, followed by
extraction with chloroform. The organic layer was
dried with MgSO₄ and then concentrated. The residue
was purified by silica gel column chromatography,
thereby obtaining 0.58 g of the above-identified
15 compound (yield: 40%).

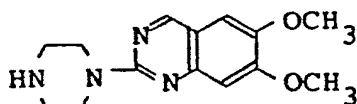
Melting point: 103 - 107°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.07 (3H,t,J=7Hz), 1.21 (3H,t,J=7Hz),
2.48 (4H,m), 3.16 (2H,s), 2.20 - 2.50 (4H),
20 3.54 (2H,s), 7.32 (5H,s), 7.59 (1H,s).

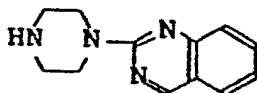
Referential Example 73:

2-Piperazino-6,7-dimethoxyquinazoline



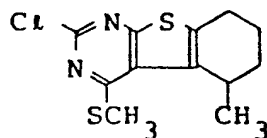
Refluxed for 2 hours in isoamyl alcohol (15 ml) were 0.63 g of 2-chloro-6,7-dimethoxyquinazoline
 5 (synthesized by the method described in Japanese Patent Laid-Open No. 36390/1972) and 0.72 g of anhydrous piperazine. Isoamyl alcohol was thereafter distilled off under reduced pressure, followed by extraction with 2N-NaOH and chloroform. The chloroform layer was
 10 washed with saturated saline and then dried with anhydrous magnesium sulfate. Chloroform was distilled off under reduced pressure to obtain 0.7 g of the intended product (yield: 91%).

The following compound was also synthesized in a
 15 similar manner.



Referential Example 74:

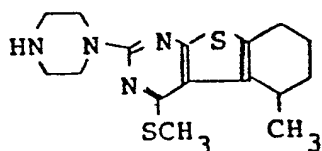
2-Chloro-5-methyl-4-methylthio-5,6,7,8-tetrahydrobenzo[1]thieno[2,3-d]pyrimidine



To 2.65 g of 2,4-dichloro-5-methyl-5,6,7,8-tetrahydrobenzo[1]thieno[2,3-d]pyrimidine [synthesized by the process described in M. Robba, P. Touzot and R.M. Riquelme, C.R. Acad. Sci. Ser. C., 276(1), 93(1973)] and 50 ml of acetone, a MeOH solution (15 ml) of 0.68 g of MeSNa which was prepared on the side was added. The resultant mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure, followed by extraction with water and chloroform. The chloroform layer was dried with magnesium sulfate and chloroform was distilled off under reduced pressure. The residue was purified by column chromatography to obtain 0.9 g of the intended product (yield: 31%).

15 Referential Example 75:

5-Methyl-4-methylthio-2-piperazino-5,6,7,8-tetrahydrobenzo[1]thieno[2,3-d]pyrimidine

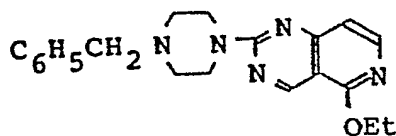


In methylene chloride, 0.9 g of the 2-chloro-5-

methy1-4-methylthio-5,6,7,8-tetrahydrobenzo[1]thieno-
[2,3-d]pyrimidine obtained in Referential Example 74,
0.35 g of 1-piperazinecarboxyaldehyde and 0.6 g of
triethylamine were reacted for 3 hours. The reaction
5 mixture was poured in water, followed by extraction
with methylene chloride. The methylene chloride layer
was dried with anhydrous magnesium sulfate and was then
concentrated under reduced pressure. The residue was
added with 10 ml of HCl-saturated ethanol and the
10 resultant mixture was stirred at 80°C for 2 hours.
After concentration of the reaction mixture, the
concentrate was extracted with chloroform. The
chloroform layer was washed with 2N-NaOH and then with
saturated saline. The chloroform layer was dried with
15 anhydrous magnesium sulfate and was then concentrated.
The residue was purified by column chromatography to
obtain 0.6 g of the intended product (yield: 58%).

Referential Example 76:

20 2-(4-Benzylpiperazino)-5-ethoxypyrido[4,3-d]-
pyrimidine



Phosphorus oxychloride (5 ml) was added to
0.56 g (1.74 mmol) of 2-(4-benzyl-1-piperazino)-5-

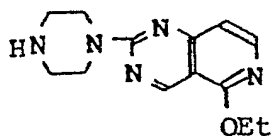
oxopyrido[4,3-d]pyrimidine. They were reacted at 110°C for 1 hour. The reaction mixture was then added dropwise to a mixture of ice, sodium hydrogencarbonate and chloroform. After decomposition, the oil layer was washed with saturated saline and then dried with sodium sulfate. After distilling off chloroform under reduced pressure, an ethanol solution (50 ml) of 1.48 g (21.7 mmol) of sodium ethoxide was added at 0°C. The resultant mixture was heated under reflux for 1 hour. After distilling off ethanol under reduced pressure, water was added, followed by extraction with ethanol. The oil layer was washed with saturated saline and then dried with sodium sulfate. Chloroform was distilled off under reduced pressure to obtain 0.55 g of light yellowish oil (yield: 90%).

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.47 (3H,t,J=8Hz), 2.54 (2H,m), 3.57 (2H,s),
4.00 (2H,m), 4.31 (2H,q,J=8Hz),
6.87 (1H,d,J=7Hz), 7.34 (5H,s),
8.04 (1H,d,J=7Hz), 9.24 (1H,s).

Referential Example 77:

5-Ethoxy-2-piperazinopyrido[4,3-d]pyrimidine



In a hydrogen atmosphere, a mixture of 0.5 g (1.43 mmol) of the 2-(4-benzylpiperazino)-5-ethoxy-pyrido[4,3-d]pyrimidine obtained in Referential Example 76, 0.05 g of 10% Pd-C and 30 ml of ethanol was heated under reflux for 5 hours. After cooling, the catalyst was filtered off and washed with ethanol. The solvent was distilled off from the mother liquor. Upon recrystallization from ethyl acetate, 0.3 g of white crystals were obtained (yield: 80%).

Melting point: 196 - 198°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

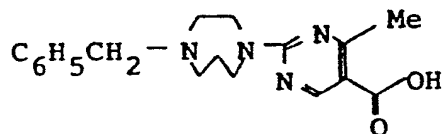
3400, 2860, 2790, 1615, 1575, 1560, 1500, 1425, 1330, 1270, 830.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.30 (3H,t,J=8Hz), 3.35 (2H,m), 4.40 (2H,m), 4.56 (2H,q,J=8Hz), 6.93 (1H,d,J=7Hz), 8.14 (1H,d,J=7Hz), 9.31 (1H,s).

Referential Example 78:

2-(4-Benzylhomopiperazino)-4-methyl-
pyrimidine-5-carboxylic acid



Dissolved in 10 ml of isoamyl alcohol were 4 g of ethyl 4-methyl-2-methylthiopyrimidine-5-carboxylate

[synthesized by the process described in Acta. Chim. Sinia., 23, 145(1957)] and 5.39 g of N-benzylhomopiperazine (synthesized by the process described in Japanese Patent Laid-Open No. 18488/1975). They were
5 reacted for 5 hours while being heated under reflux. Thereafter, isoamyl alcohol and excess N-benzylhomopiperazine were distilled off under reduced pressure. The residue was added with 3.4 g of potassium hydroxide and 40 ml of ethanol. While being heated under
10 reflux, they were reacted for 2.5 hours. After cooling the reaction mixture, ethanol was distilled off. The residue was dissolved in water and the resultant aqueous solution was adjusted to pH 3 - 4 with conc. hydrochloric acid. By filtration, 2.70 g of the
15 intended product was obtained as crystals. Yield: 44% (based on 5-ethoxycarbonyl-6-methyl-2-methylthio-pyrimidine).

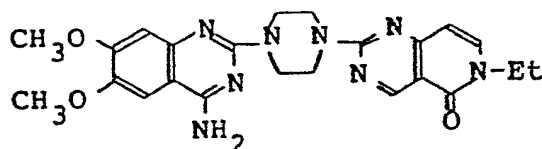
Melting point: 77 - 80°C.

¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

20 2.20 (2H,m), 2.60 (3H,s), 3.32 (8H,m),
 4.28 (2H,s), 7.46 (5H,s), 8.76 (1H,s).

Example 1:

4-Amino-6,7-dimethoxy-2-(4-(5,6-dihydro-
6-ethyl-5-oxopyrido[4,3-d]pyrimidin-2-yl)-
piperazino)quinazoline and acid addition
5 salts thereof



In 600 ml of isoamyl alcohol as a solvent,
24.5 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline,
27.8 g of the 5,6-dihydro-6-ethyl-5-oxo-2-piperazino-
pyrido[4,3-d]pyrimidine and 10.8 g of triethylamine
10 were refluxed for 4 hours. After allowing the reaction
mixture to cool down, the precipitated crystals were
collected by filtration. The crystals were then
recrystallized from a mixed solvent of methanol and
dichloromethane to obtain 39.4 g of the intended
15 product (melting point: 255 - 259°C; yield: 83%).

¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

1.25 (3H,t,J=7Hz), 3.88 (16H,m),
6.27 (1H,d,J=8Hz), 6.79 (1H,s), 7.12 (2H,br.s),
7.44 (1H,s), 7.72 (1H,d,J=8Hz), 9.08 (1H,s).

20 Dissolved in methanol-chloroform was 33.4 g of
the free base obtained in the above preparation
process, followed by an addition of equimolar amount of

HCl in ethanol. Thereafter, excess hydrogen chloride and solvent were distilled off to obtain 36 g of the hydrochloride of the above-identified compound.

Melting point: 273 - 275°C.

5 ^1H -NMR spectrum (DMSO- d_6 solution, δ ppm):

1.22 (3H,t,J=7Hz), 3.84 (3H,s), 4.02 (10H,m),
6.22 (1H,d,J=8Hz), 7.62 (1H,s),
7.67 (1H,d,J=8Hz), 7.68 (1H,s), 8.54 (1H,br.s),
8.90 (1H,br.s), 9.03 (1H,s), 12.42 (1H,br.s).

10 IR spectrum (KBr tablet, cm^{-1}):

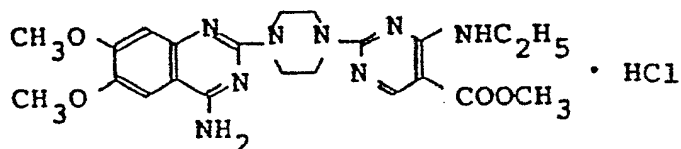
1635, 1620, 1590, 1570, 1245.

Each of the following acid addition salts was synthesized in a similar manner.

15	Acetate	m.p. 255 - 256°C
	Fumarate	m.p. 242 - 244°C
	Maleate	m.p. 242 - 244°C
	Benzoate	m.p. 224 - 226°C
	Citrate	m.p. 222 - 226°C
20	Tartrate	m.p. 237 - 241°C
	Hydrogenbromide	m.p. 249 - 252°C
	Methanesulfonate	m.p. >300°C
	Sulfate	m.p. 278 - 280°C
	Phosphate	m.p. 292 - 295°C

Example 2:

4-Amino-6,7-dimethoxy-2-(4-(4-ethylamino-5-methoxycarbonylpyrimidine-2-yl)piperazino)-quinazoline hydrochloride



5 In 20 ml of n-butanol, 1.1 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline and 1.22 g of the 4-ethylamino-5-methoxycarbonyl-2-piperazinopyrimidine obtained in Referential Example 69 were refluxed for 4 hours. After allowing the reaction mixture to cool
10 down, the precipitated crystals were collected by filtration. The crystals were washed with ethanol and then with ethyl acetate to obtain 1.8 g of the above-identified compound (yield: 78%).

Melting point: 269 - 270°C (decomposed).

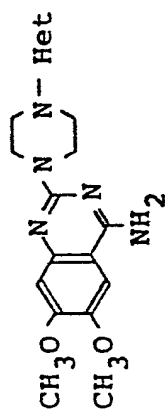
15 ¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

1.2 (3H,t,J=7Hz), 3.78 (3H,s), 3.86 (3H,s),
3.92 (3H,s), 3.97 (8H,m), 7.43 (1H,s),
7.74 (1H,s), 8.54 (1H,s).

Examples 3 to 80:

Following the procedure of Example 1 or 2, a variety of compounds of this invention were prepared. Results are summarized in Table 1, in which Preparation Processes A and B correspond to Examples 1 and 2 respectively. In addition, the number of one of the Referential Example is given in parenthesis under each Preparation Process. This number indicates the Referential Example in which the corresponding starting material was prepared.

Table 1



Ex. No.	Het	Prep'n (Ref.Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
3		B (14)	50	HCl salt >300	CDCI ₃ -CD ₃ OD 3.98(3H,s), 4.04(3H,s), 4.08(8H,m), 6.40(1H,d,J=8Hz), 7.32(1H,s), 7.34 (1H,s), 7.40(1H,d,J=8Hz), 9.24(1H,s).	KBr tablet 3425, 3155, 1645, 1625, 1578, 1496, 1432, 1250, 1238, 1109, 984.
4		B (14)	79	HCl salt 277-278	DMSO-d ₆ 3.44(3H,s), 3.86(3H,s), 3.92(3H,s), 4.05(8H,m), 6.31(1H,d,J=8Hz), 7.50 (1H,s), 7.76(1H,s), 7.80 (1H,d,J=8Hz), 8.78(2H,br.s), 9.12(1H,s)	

Table 1 (Cont'd)

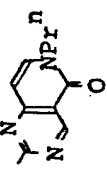
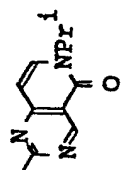
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
5		B (14)	97	HCl salt 269 (dec'd)	DMSO-d ₆ 0.89(3H, t, J=7Hz), 1.48- 1.80(2H, m), 3.40(2H, t, J=7Hz), 3.89(3H, s), 3.91 (3H, s), 4.08(8H, br. s), 6.27 (1H, d, J= 8Hz), 7.72(1H, s), 7.78(1H, s), 7.79(1H, d, J= 8Hz), 8.68(2H, br. s), 9.07 (1H, s), 12.61(1H, br. s).	KBr tablet 3330, 3180, 1642, 1628, 1596, 1576, 1506, 1440, 1248.
6		B (14)	68	HCl salt 276 (dec'd)	DMSO-d ₆ 1.33(6H, d, J=8Hz), 3.87(3H, s), 3.91(3H, s), 4.07(8H, br. s), 5.07(1H, septet, J= 8Hz), 6.35(1H, d, J=9Hz), 7.65(1H, s), 7.77(1H, s), 7.86(1H, d, J=9Hz), 8.77 (2H, br. s), 9.11(1H, s).	KBr tablet 3340, 3170, 1642, 1598, 1576, 1514, 1442, 1246.

Table 1 (Cont'd)

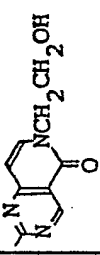
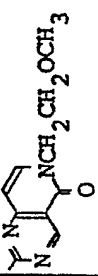
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
7		B (16)	39	HCl salt 260-262 (dec'd)	DMSO-d ₆ 3.7(4H, br.), 3.86(3H, s), 3.90(3H, s), 4.05(8H, br.), 6.30(1H, d, J=7Hz), 7.58 (1H, s), 7.70(1H, d, J= 7Hz), 7.75(1H, s), 8.8(2H), 9.10(1H, s).	KBr tablet 3320, 3170, 1620, 1590, 1570.
8		B (14)	14	HCl salt 274	DMSO-d ₆ 3.30(3H, s), 3.88(3H, s), 3.91(3H, s), 4.04(10H, m), 6.50(1H, d, J=7Hz), 7.40- 7.68(3H, m), 9.10(1H, s).	Nujol 3300, 3100, 1640, 1376, 1107.

Table 1 (Cont'd)

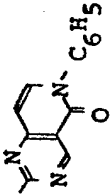
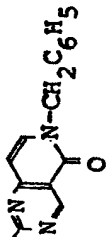
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
9		B (14)	57	HCl salt 291-293 (dec'd)	DMSO-d ₆ 3.85(3H,s), 3.90(3H,s), 4.04(8H,br.s), 6.39(1H,d, J=8Hz), 7.3-7.6(5H), 7.6- 7.9(3H), 8.6(2H,br.s), 9.13(1H,s).	KBr tablet 3180, 1630, 1580, 1500.
10		B (14)	57	HCl salt 269-270 (dec'd)	CDCl ₃ 3.86(3H,s), 3.89(3H,s), 4.04(8H,m), 5.11(2H,s), 6.34 (1H,d, J=7Hz), 7.32(5H,s), 7.62(1H,s), 7.76(1H,s), 7.88(1H,d, J=7Hz), 8.80(2H, br.s), 9.11(1H,s).	KBr tablet 3340, 3200, 1640, 1620, 1595, 1570.

Table 1 (Cont'd)

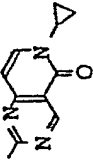
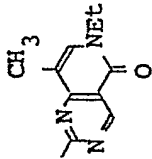
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
11		B (14)	30	Free base	CDCl ₃ 1.07(4H,m), 3.24(1H,m), 3.86(14H,m), 5.38(2H,br.s), 6.27(1H,d,J=8Hz), 6.88 (1H,s), 6.94(1H,s), 7.33 (1H,d,J=8Hz), 9.26(1H,s).	
					m.p. 263-265 (dec'd)	
12		B (14)	85	HCl salt 280-292 (dec'd)	DMSO-d ₆ 1.23(3H,t,J=7Hz), 2.15 (3H,d,J=0.9Hz), 3.85(3H, s), 3.91(3H,s), 3.8-4.2 (10H,m), 7.32(1H,br.s), 7.69 (1H,br.s), 7.73(1H,br.s), 8.65(2H,br.s), 9.11(1H,s).	KBr tablet 1650, 1638, 1594, 1577, 1501, 1437, 1251, 1115, 989.

Table 1 (Cont'd)

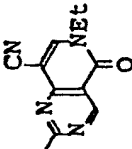
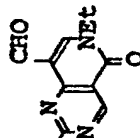
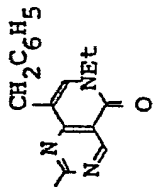
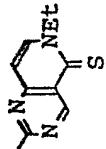
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
13		B (24)	55	HCl salt >300	DMSO-d ₆ 1.29(3H,t,J=7Hz), 3.88(3H,s), 3.92(3H,s), 3.9-4.1(10H,m), 7.34(1H,s), 7.69(1H,s), 8.40(2H,br.s), 8.8(1H,s), 9.12(1H,s).	KBr tablet 2230, 1678, 1619, 1600, 1578, 1520, 1436, 1253, 1107, 996, 810.
14		B (23)	56	HCl salt >300	DMSO-d ₆ 1.27(3H,t,J=7Hz), 3.84(3H,s), 3.89(3H,s), 4.02(8H,m), 7.12(1H,s), 7.63(1H,s), 8.58(1H,s), 9.14(1H,s), 10.49(1H,s).	Nujol 3330, 3160, 1685, 1668, 1604.

Table 1 (Cont'd)

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
15		B (14)	69	HCl salt 256.5	DMSO-d ₆ 1.25(3H,t,J=6Hz), 3.88(3H,s), 3.92(3H,s), 3.92-4.20(10H,m), 7.20-7.40(5H,m), 7.56(1H,s), 7.54(1H,s), 8.88(1H,s), 8.70(1H,m), 9.08(1H,s).	KBr tablet 3300, 3150, 1650, 1598, 1490, 1430, 1390, 1345, 1248, 1112, 983.
16		B (25)	36	Free base 158-162	CDC1 ₃ 1.46(3H,t,J=7Hz), 3.90(14H,m), 4.59(2H,t,J=7Hz), 5.24(2H,br.s), 6.64(1H,d,J=7Hz), 6.83(1H,s), 6.97(1H,s), 7.52(1H,d,J=7Hz), 9.87(1H,s).	

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Table 1 (Cont'd)

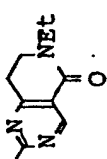
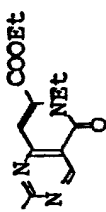
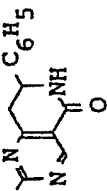
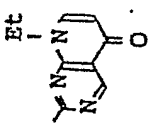
Ex. No.	Het	prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
17		A (39)	48	Free base 268-270	CDCl ₃ -CD ₃ OD 1.23(3H,t,J=7Hz), 2.98 (2H,t,J=8Hz), 3.62(4H,m), 4.00(14H,m), 7.20(1H,s), 7.36(1H,s), 8.80(1H,s).	
18		B (14)	61	HCl salt 275-276		KBr tablet 3320, 3145, 1734, 1678, 1636, 1604, 1576, 1538.

Table 1 (Cont'd)

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
19		B (14)	60	287 (dec'd)	DMSO-d ₆ 3.12(2H, br. d, J=6Hz), 3.87(3H, s), 3.92(3H, s), 4.05(8H, br. s), 4.77(1H, t, J=6Hz), 7.19(5H, s), 7.63 (1H, s), 7.78(1H, s), 8.43 (1H, br. s), 8.55(1H, s), 8.76(2H, br. s), 12.48(1H, br. s).	KBr tablet 3345, 3180, 1590, 1514, 1254.
20		A*	76	Free base	DMSO-d ₆ 1.32(3H, t, J=7Hz), 3.80(3H, s), 3.88(3H, s), 3.82(8H, br. s), 4.16(2H, q, J=7Hz), 5.98 (1H, d, J=8Hz), 6.74(1H, s), 7.13(2H, br. s), 7.44(1H, s), 7.87(1H, d, J=8Hz), 8.98(1H, s).	
				HCl salt 259 (dec'd)		

*The raw material, 5,8-dihydro-8-ethyl-5-oxo-2-piperazinopyrido[2,3-d]pyrimidine, was synthesized by the process described in Japanese Patent Laid-Open No. 18600/1978.

Table 1 (Cont'd)

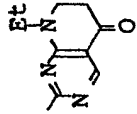
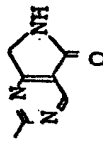
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
21		A (56)	82	HCl salt 287-288	DMSO-d ₆ 1.16(3H,t,J=7Hz), 2.72(2H,t,J=7Hz), 3.44(4H), 3.90(8H,br.s), 4.08(6H,s), 7.78(1H,s), 7.84(1H,s), 8.21(1H,s), 8.71(1H,br.s), 9.11(1H,br.s), 12.80(1H,br.s).	
22		B (43)	91	HCl salt 300 (dec'd)	Not measured due to insolubility in DMSO MASS 422(M ⁺ -HCl)	KBr tablet 3300, 3160, 2900, 1705, 1605, 1585, 1328, 1245, 1112, 1020, 985, 835.

Table 1 (Cont'd)

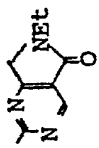
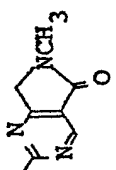
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
23		B (45)	92	HCl salt 272 (dec'd)	DMSO-d ₆ 1.17(3H,t,J=9Hz), 3.20-3.60(10H,m), 3.88(3H,s), 3.92(3H,s), 4.40(2H,s), 7.57(1H,s), 7.76(1H,s), 8.66(1H,s), 8.90(2H,br.s).	KBr tablet 3290, 1663, 1590, 1510, 1430, 1253, 1112, 984, 870, 793.
24		B (45)	94	HCl salt 280-281 (dec'd)	DMSO-d ₆ 3.04(3H,s), 3.88(3H,s), 3.94(3H,s), 4.05(8H,m), 4.42(2H,s), 7.44(1H,s), 7.78(1H,s), 8.72(1H,s), 8.76(2H,brs).	Nujol 3600-2700, 1665, 1615, 1598, 1520, 1260.

Table 1 (Cont'd)

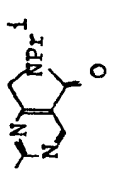
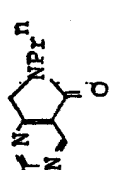
Ex. No.	Het	Prep'n (Ref.Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
25		B (45)	76	HCl salt 263-264	DMSO-d ₆ 1.22(6H,d,J=7Hz), 3.88(3H,s), 3.94(3H,s), 4.05(8H,m), 4.38(3H,m), 7.48(1H,s), 7.78(1H,s), 8.72(1H,s), 8.80(2H,br.s).	Nujol 3400-2600, 1665, 1615, 1595, 1515, 1254, 1232, 986.
26		B (45)	63	HCl salt 250-252	DMSO-d ₆ 0.87(3H,t,J=7Hz), 1.60(2H, hextet, J=7Hz), 3.43(2H,t, J=7Hz), 3.88(3H,s), 3.92(3H,s), 4.06(8H,s), 4.41(2H,s), 7.64(1H,s), 7.81(1H,s), 8.72(1H,s), 8.73(1H,br.), 8.99(1H,br.), 12.46(1H,br.).	KBr tablet 3390, 3120, 2960, 2930, 2870, 1660, 1615, 1590, 1515, 1435, 1255, 1110, 985.

Table 1 (Cont'd)

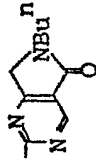
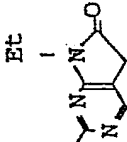
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
27		B (45)	47	HCl salt 263-265	DMSO-d ₆ 0.92(3H,t,J=7Hz), 1.05-1.76(4H), 3.47(2H,t,J=7Hz), 3.89(3H,s), 3.92(3H,s), 4.08(8H,s), 4.41(2H,s), 7.68(1H,s), 7.82(1H,s), 8.70(1H,s), 8.73(1H,br), 9.01(1H,br), 12.55(1H,br).	KBr tablet 3350, 3120, 2950, 2870, 1660, 1615, 1590, 1510, 1435, 1260, 1230, 1110, 985.
28		B (55)	72	HCl salt 284-285	DMSO-d ₆ 1.20(3H,t,J=7Hz), 3.50(2H,s), 3.68(2H,q,J=7Hz), 3.87(3H,s), 3.89(3H,s), 3.93(8H,br.s), 7.61(1H,s), 7.75(1H,s), 8.01(1H,s), 8.68(2H,br.s).	

Table 1 (Cont'd)

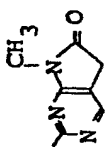
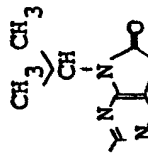
Ex. No.	Het	Prep'n (Ref.Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
29		B (55)	73	HCl salt >300	DMSO-d ₆ 3.12(3H,s), 3.50(2H,s), 3.88(14H,m), 7.50(1H,s), 7.70(1H,s), 8.03(1H,s).	KBr tablet 3125, 1735, 1670, 1635, 1605, 990.
30		B (55)	66	HCl salt 284 (dec'd)	CD ₃ OD-CDCl ₃ 1.54(6H,d,J=7Hz), 3.42(2H,s), 3.98(3H,s), 4.03(1H,m), 7.36(1H,s), 7.57(1H,s), 7.98(1H,s).	KBr tablet 3380, 3160, 1745, 1660, 1630, 1595, 1445, 1118.

Table 1 (Cont'd)

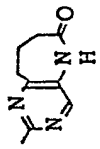
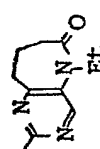
Ex. No.	Het	Prep'n (Ref.Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
31		B (53)	61	HCl salt 300 (dec'd)	DMSO-d ₆ 2.1-2.3(4H,m), 2.6-2.9(2H,m), 3.85(3H,s), 3.90(3H,s), 3.7-4.2(8H,m), 7.52(1H,s), 7.74(1H,s), 8.03(1H,s), 8.73(2H,br.s), 9.30(1H,s).	Nujol 3180, 1690, 1655, 1630, 1590, 1255.
32		B (53)	71	HCl salt 228.5	DMSO-d ₆ 1.02(3H,t,J=9Hz), 2.10-2.30(4H,m), 2.68(2H,br.s), 3.20-3.50(10H,m), 3.85(3H,s), 3.96(3H,s), 7.56(1H,s), 7.74(1H,s), 8.38(H,s), 8.66(1H,br.s), 8.90(1H,br.s).	KBr tablet 3450, 3330, 3160, 2960, 1632, 1585, 1435, 1255, 1110, 985, 850, 770.

Table 1 (Cont'd)

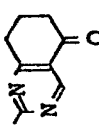
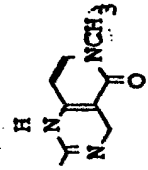
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
33		B (48)	47	HCl salt 279-280	DMSO-d ₆ 2.06(2H,m), 2.58(2H,m), 2.88(2H,m), 3.88(3H,s), 3.92(3H,s), 3.46(8H,br. s), 7.55(1H,s), 7.78(1H,s), 8.79(1H,s)..	KBr tablet 3350(broad), 3160(broad), 1655, 1578, 1515.
34		B (32)	40	HCl salt 260-265 (dec'd)	DMSO-d ₆ -CD ₃ OD 3.47(3H,s), 3.94(14H,m), 4.28(2H,s), 6.36(1H,d, J= 8Hz), 7.36(1H,s), 7.66(1H,d, J=8Hz), 7.68(1H,s).	

Table 1 (Cont'd)

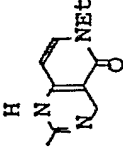
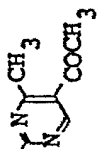
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
35		A (32)	25	Free base	CDCl ₃ -CD ₃ OD 1.32(3H,t,J=7Hz), 3.9(16H,m), 4.32(2H,s), 6.06(1H,d,J=8Hz), 6.92(1H,s), 7.15(1H,d,J=8Hz), 7.20(1H,s).	
				HCl salt 260-264		
36		B (10)	92	HCl salt 293-294 (dec'd)	DMSO-d ₆ 2.49(3H,s), 2.58(3H,s), 3.87(3H,s), 3.91(3H,s), 4.04(8H,br.s), 7.60(1H,s), 7.75(1H,s), 8.62(1H,br.s), 8.87(2H,br.s), 11.34(1H,br.s).	

Table 1 (Cont'd)



Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
37		B (30)	90	HCl salt 271-276 (dec'd)	DMSO-d ₆ 1.13(3H, t, J=7Hz), 3.40(2H, dq, J=5.3, 7.0Hz), 3.88(3H, s), 3.93(3H, s), 4.00(8H, br. s), 7.40(1H, br. s), 7.71(1H, br. s), 8.40(1H, br. s), 8.60(1H, br. s), 8.83(2H, s), 8.83(1H, br. t).	
38		B (10)	42	HCl salt 254-256 (dec'd)	DMSO-d ₆ 1.12(3H, t, J=7Hz), 1.20(3H, t, J=7Hz), 2.82(2H, q, J=7Hz), 3.5(2H, m), 3.86(3H, s), 3.90(3H, s), 4.00(8H, m), 7.54(1H, s), 7.75(1H, s), 8.38(1H, s).	KBr tablet 3320, 3160, 1630, 1580.

Table 1 (Cont'd)

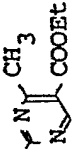
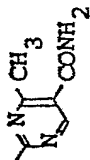
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
39		A (10)	78	Free base	CDCl ₃ 1.36(3H, t, J=7Hz), 2.67(3H, s), 3.95(14H, m), 4.31(2H, q, J=7Hz), 5.24(2H, br. s), 6.82(1H, s), 6.95(1H, s), 8.84(1H, s).	
40		B (10)	80	HCl salt >300	DMSO-d ₆ 2.51(3H, s), 3.91(6H, m), 3.97(6H, s), 7.46(1H, s), 7.72(1H, s), 8.50(1H, s), 8.70(2H, br. s).	KBr tablet 3340, 3160, 1650, 1626, 1585.

Table 1 (Cont'd)

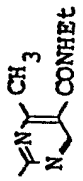
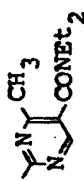
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
41		B (10)	30	Free base	CDCl ₃ 1.23(3H, t, J=8Hz), 2.52 (3H, 2), 3.44(2H, m), 3.90 (14H, m), 5.4(2H, br. s), 5.92(1H, br. s), 6.88(1H, s), 6.94(1H, s), 8.34(1H, s)	
42		B (10)	23	212 (dec'd)	HCl salt 283-286	KBr tablet 3380, 1630, 1594, 1534, 1440, 1278, 1256, 1240.

Table 1 (Cont'd)

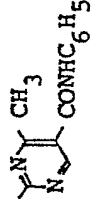
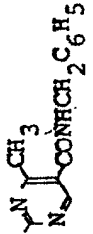
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
43		B (10)	69	HCl salt 250	DMSO-d ₆ 2.51(3H,s), 3.87(3H,s), 3.89(3H,s), 4.03(8H,m), 7.00-7.45(3H,m), 7.60-7.86 (4H,m), 8.55(1H,s), 8.74 (2H,br.s), 10.30(1H,s).	Nujol 3455, 3180, 3120, 1630, 1598.
44		B (10)	61	HCl salt 277	DMSO-d ₆ 2.48(3H,s), 3.73(3H,s), 3.89(3H,s), 3.80-4.20 (8H,br.s), 4.23(2H,d, J=5.6Hz), 7.34(5H,s), 7.58(1H,s), 7.74(1H,s), 8.50(1H,s), 8.80(2H,br.s)	Nujol 3415, 3260, 3100, 1630, 1587.

Table 1 (Cont'd)

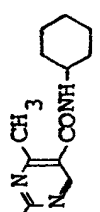
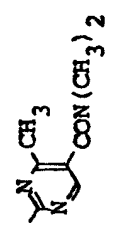
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
45		B (10)	62	HCl salt 275-276 (dec'd)	CDCI ₃ 1.0-2.0(10H), 2.44(3H,s), 3.85(3H,s), 3.90(3H,s), 3.97(8H,br.s), 4.00(1H), 7.56(1H,s), 7.75(1H,s), 8.08 (1H,d,J=8Hz), 8.36(1H,s), 8.80(2H,br.s).	KBr tablet 3280, 1630, 1585.
46		B (10)	65	HCl salt 212-215	DMSO-d ₆ 2.28(3H,s), 2.94(6H,br.s), 3.86(3H,s), 3.90(3H,s), 3.97 (8H,m), 7.62(1H,s), 7.78(1H, s), 8.26(1H,s), 8.70(1H,br. s), 8.94(1H,br.s).	

Table 1 (Cont'd)

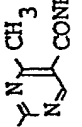
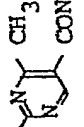
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
47	 <chem>CC1=CN=CN=C1C(=O)N</chem>	B (10)	44	HCl salt 282-284 (dec'd)	DMSO-d ₆ 2.43(3H,s), 2.59(6H,s), 3.85(3H,s), 3.90(3H,s), 3.97(8H,br.s), 7.55(1H,s), 7.66(1H,s), 8.35(1H,s).	
48	 <chem>CC1=CN=CN=C1C(=O)N.CF3S(=O)(=O)C1=CC=CC=C1</chem>	B (10)	39	HCl salt 194-197 (dec'd)	DMSO-d ₆ 2.47(3H,s), 3.84(3H,s), 3.89(3H,s), 3.96(10H), 7.38 (1H,br.s), 7.70(1H,br.s), 8.47(1H,s), 8.70(1H,br.s), 8.90(1H,br.s), 8.93(1H,br.t, J=5.5Hz).	

Table 1 (Cont'd)

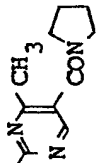

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
49		B (10)	77	HCl salt 246.5	DMSO-d ₆ 1.88(4H, br. s), 2.35(3H, s), 3.18-3.60(4H, m), 3.88(3H, s), 3.91(3H, s), 3.99(8H, br. s), 7.60(1H, s), 7.77(1H, s), 8.32(1H, s), 8.60(2H, br. s).	KBr tablet 3450, 3120, 1628, 1580, 1526, 1435, 1255, 1110, 985.
50		B (69)	75	HCl salt 255-257	DMSO-d ₆ 1.28(3H, t, J=7Hz), 3.86(3H, s), 3.90(3H, s), 3.98(8H, br. s), 4.22(2H, q, J=7Hz), 7.53(1H, s), 7.74(1H, s), 8.49(1H, s), 8.65(1H, br. s), 8.92(1H, br. s), 12.27(1H, br. s).	

Table 1 (Cont'd)

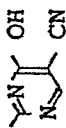
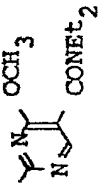
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
51		A (69)	15	Free base	CDCl ₃ -CD ₃ OD 3.97(14H,m), 7.08(1H,s), 7.30(1H,s), 8.10(1H,s).	
				HCl salt 287-290		
52		B (69)	85	HCl salt 278-281 (dec'd)	DMSO-d ₆ 1.27(6H,br.t,J=6Hz), 3.50 (4H,br.q,J=6Hz), 4.07(9H, br.s), 4.18(8H,br.s), 7.92 (1H,s), 8.01(1H,s), 9.34(1H, s), 8.87(1H,br.s), 9.22(1H, br.s).	

Table 1 (Cont'd)

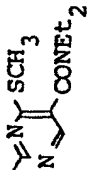
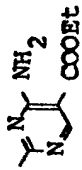
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
53		B (69)	51	HCl salt 226-227	DMSO-d ₆ 1.14(3H, t, J=7Hz), 1.22(3H, t, J=7Hz), 2.56(3H, s), 3.35(4H, m), 3.92(6H, m), 4.04(8H, m), 7.72(1H, s), 7.83(1H, s), 8.10(1H, s), 8.69(1H, br. s), 9.01(1H, br. s).	
54		A (69)	84	Free base 271-272	CDCl ₃ -CD ₃ OD 1.37(3H, t, J=7Hz), 4.00(14H, m), 4.31(2H, q, J=7Hz), 7.48(1H, s), 7.53(1H, s), 8.63(1H, s).	
				HCl salt 240-245	CDCl ₃ -CD ₃ OD 1.40(3H, t, J=7Hz), 3.98(3H, s), 4.04(3H, s), 4.12(8H, m), 4.40(2H, q, J=7Hz), 7.52(1H, s), 7.57(1H, s), 8.53(1H, s).	

Table 1 (Cont'd)

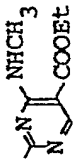
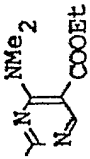
Ex. No.	Het	Prep'n (Ref.Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
55		B (69)	82	HCl salt 274-276	DMSO-d ₆ 1.29(3H,t,J=8Hz), 2.96(3H,d,J=5Hz), 3.86(3H,s), 3.90(3H,s), 3.99(8H,br.s), 4.22(2H,q,J=8Hz), 7.56(1H,s), 7.73(1H,s), 8.09(1H,br.d,J=5Hz), 8.49(1H,s), 8.63(1H,br.s), 8.88(1H,br.s), 12.28(1H,br.s).	
56		B (69)	54	HCl salt 275-277	DMSO-d ₆ 1.26(3H,t,J=7Hz), 3.0(6H,s), 3.87(3H,s), 3.90(3H,s), 3.98(8H,m), 4.22(2H,q,J=7Hz), 7.62(1H,s), 7.78(1H,s), 8.36(1H,s), 8.66(1H,br.s), 8.94(1H,br.s).	

Table 1 (Cont'd)

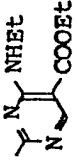
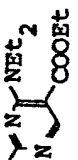
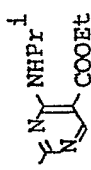
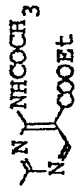
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
57		A (69)	46	Free base 223-227	CDCl ₃ 1.25(3H, t, J=7Hz), 1.34(3H, t, J=7Hz), 3.52(2H, d, q, J=5.7Hz), 3.91(3H, s), 3.94(3H, s), 3.96(8H, s), 4.27(2H, q, J=7Hz), 5.23(2H, br. s), 6.82(1H, s), 6.93(1H, s), 8.03(1H, br. t, J=5Hz), 8.62(1H, s).	
				HCl salt 223-225		
58		B (69)	50	Free base	CDCl ₃ 1.22(6H, t, J=7Hz), 1.34(3H, t, J=7Hz), 3.47(4H, q, J=7Hz), 3.92(8H, m), 3.94(3H, s), 3.97(3H, s), 3.97(3H, s), 4.28(2H, q, J=7Hz), 5.28(2H, br. s), 6.83(1H, s), 6.94(1H, s), 8.50(1H, s).	
				HCl salt 280-282		

Table 1 (Cont'd)

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
59		B (69)	91	Free base	CDCl ₃ 1.27(6H, d, J=7Hz), 1.34(3H, t, J=7Hz), 3.96(14H, m), 4.26(2H, q, J=7Hz), 4.26(1H, m), 5.22(2H, br. s), 6.82(1H, s), 6.95(1H, s), 7.95(1H, d, J=7Hz), 8.63(1H, s).	
60		A (69)	49	Free base 276-277	CDCl ₃ -CD ₃ OD 1.40(3H, t, J=7Hz), 2.50(3H, s), 3.98(3H, s), 4.03(3H, s), 4.07(8H, m), 4.40(2H, q, J=7Hz), 7.47(1H, s), 7.54(1H, s), 8.85(1H, s).	
				HCl salt 260-263		
				HCl salt 234-237		

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1,2

NMR spectrum, δ ppm	IR spectrum (cm^{-1})
<p>50-d₆</p> <p>2.4(3H,t,J=7Hz), 1.36(6H,d, 5Hz), 3.62(2H,J=7Hz), 3.89(H,s), 3.93(3H,s), 4.10(8H, s), 5.14(1H,heptet,J=6Hz), 7.0(1H,s), 7.79(1H,s), 8.38(1,s), 8.64(2H,br.s), 8.98(1,s).</p>	
<p>50-d₆</p> <p>1.6(6H,d,J=6Hz), 3.99(3H,s), 3.9(3H,s), 4.13(3H,s), 4.2(8H,m), 4.50(1H,m), 5.1(1H,s), 7.97(1H,s), 8.1(1H,d,J=7Hz), 8.73(1H,s), 9.0(1H,br.s), 9.11(1H,br.s).</p>	

Table 1 (Cont'd)

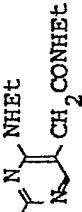
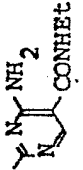
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
63		B (69)	51	HCl salt 257-258 (dec'd)	DMSO-d ₆ 1.03(3H, t, J=8Hz), 1.18(3H, t, J=8Hz), 3.20(4H), 3.88(14H), 7.37(2H, br. s), 7.63(1H, s), 7.68(1H, s), 8.20(1H, br. t, J=7Hz), 8.36(1H, br. s).	
64		A (69)	55	Free base 273-275	CDCl ₃ -CD ₃ OD 1.24(3H, t, J=7Hz), 3.40(2H, q, J=7Hz), 3.97(3H, s), 4.04(3H, s), 4.06(8H, m), 7.52(1H, s), 7.57(1H, s), 8.36(1H, s).	
				HCl salt 280-283		

Table 1 (Cont'd)

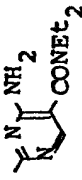

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
65		A (69)	48	Free base 285-286	CDCI ₃ 1.22(6H, t, J=7Hz), 3.46(4H, q, J=7Hz), 3.90(8H, m), 3.93(3H, s), 3.97(3H, s), 5.37(2H, br. s), 5.78(2H, br. s), 6.86(1H, s), 7.02(1H, s), 8.00(1H, s).	
66		B (69)	65	HCl salt 289-290	DMSO-d ₆ 1.13(3H, t, J=7Hz), 1.21(3H, t, J=7Hz), 3.22(2H, q, J=7Hz), 3.46(2H, q, J=7Hz), 3.87(3H, s), 3.90(3H, s), 4.03(8H, br. s), 7.64(1H, s), 7.76(1H, s), 8.50(1H, s), 8.62(2H, br. s), 8.92(1H, br. s), 9.48(1H, br. s), 12.42(1H, br. s).	

Table 1 (Cont'd)

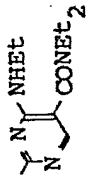

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
67		B (69)	about 100	HCl salt 236-237	CDCl ₃ 1.20(9H), 3.42(6H), 3.91(6H, s), 4.09(8H, br.s), 7.80(2H, br.s), 8.28(2H, br.s), 8.64 (1H, br.s), 9.08(1H, br.s), 12.74(1H, br.s).	
68		B (69)	48	HCl salt 296-299 (dec'd)	CD ₃ OD 2.87(3H, s), 3.06(3H, s), 3.98 (3H, s), 4.04(1H, s), 7.31 (1H, s), 7.58(1H, s), 8.27 (1H, s).	

Table 1 (Cont'd)



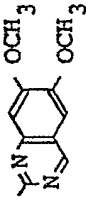
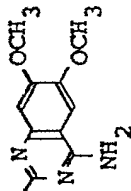
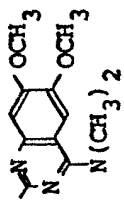
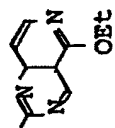
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
69		B (69)	58	HCl salt 260-262 (dec'd)	DMSO-d ₆ 3.00(9H,s), 3.88(3H,s), 3.92(3H,s), 4.07(8H,br.s), 7.65(1H,s), 7.75(1H,s), 8.19(1H,s), 8.25(1H,br.s), 8.61(1H,br.s), 8.88(1H,br.s), 12.46(1H,br.s).	
70		B (73)	82	Free base	CDCl ₃ 3.92(3H,s), 3.98(3H,s), 4.02(8H,m), 6.84(1H,s), 6.98(1H,s), 7.2(1H,m), 7.64(3H,m), 9.02(1H,s).	
				HCl salt 284-285		

Table 1 (Cont'd)

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
71		B (73)	50	Free base	CDCl ₃ 3.90(20H,m), 5.55(2H,br.s), 6.90(2H,s), 6.96(1H,s), 6.98 (1H,s), 8.82(1H,s)	
				HCl salt 295-300		
72		A**	60	Free base	DMSO-d ₆ 3.80(12H,s), 3.85(8H,s), 6.78(2H,s), 7.18(4H,br.s), 7.44(2H,s).	
				HCl salt >300		KBr tablet 1640, 1625, 1585, 1523, 1275, 1250.

** The raw material, 4-amino-6,7-dimethoxy-2-piperazinoquinazoline, was synthesized by the process described in J. Chem. Soc., 1965, 1759 and J. Med. Chem., 20, 146(1977).

Table 1 (Cont'd)

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
73		A***	56	Free base	CDCl ₃ -CD ₃ OD 3.44(6H,s), 4.00(20H,m), 7.30(1H,s), 7.35(1H,s), 7.48(1H,s), 7.50(1H,s).	
				HCl salt		
				262-263		
74		A (77)	13	Free base	CDCl ₃ 1.68(3H,t, J=8Hz), 3.92(3H,s), 3.98(9H,s), 4.54(2H,q, J=8Hz), 5.34(2H,br.s), 6.85(1H,s), 6.94(1H,d, J=7Hz), 6.97(1H,s), 8.07(1H,d, J=7Hz), 9.28(1H,s)	
				HCl salt		
				>300		

*** The raw material, 4-dimethylamino-6,7-dimethoxy-2-piperazinoquinazoline, was synthesized by the process described in J. Chem. Soc., 1965, 1759 and J. Med. Chem., 20, 146 (1977).

Table 1 (Cont'd)

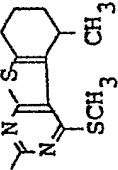
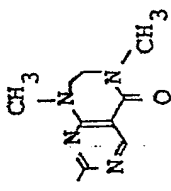
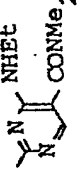

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
75		B (75)	83	HCl salt 250 (dec'd)	CDCl ₃ -DMSO-d ₆ 1.32(3H,d,J=7Hz), 1.88(4H,m), 2.68(3H,s), 2.70(2H,m), 3.45(1H,m), 3.97(3H,s), 4.01(3H,s), 4.18(8H,m), 7.78(1H,s), 8.03(1H,s).	
76		B (59)	43	HCl salt 265-269	CD ₃ OD-CDCl ₃ 3.14(3H,s), 3.23(3H,s), 3.69(4H,br.s), 4.0(14H,m), 7.23(1H,s), 7.56(1H,s), 8.62(1H,s).	KBr tablet 1595, 1480, 1234.

Table 1 (Cont'd)

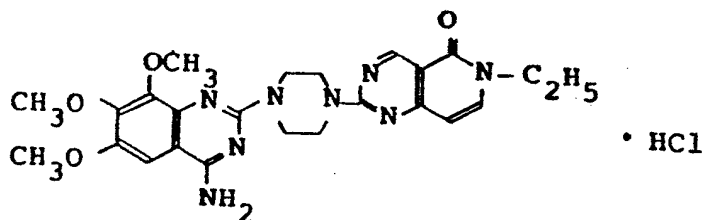
Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
77		B (69)	70	HCl salt 271-272	CD ₃ OD-CDCl ₃ 1.24(6H,t,J=7Hz), 3.0(3H,s), 3.48(4H,q,J=7Hz), 4.0(14H,m), 7.33(1H,s), 7.56(1H,s), 7.85(1H,s).	KBr tablet 3375, 3170, 1625, 1582, 1110.
78		B (69)	82	HCl salt 261-264	DMSO-d ₆ -CDCl ₃ 1.20(6H,m), 3.40(4H,m), 3.90(15H,m), 7.54(1H,s), 7.74(1H,s), 7.86(1H,s), 8.70(2H,br.s).	KBr tablet 3200, 3108, 2956, 1578, 1478, 1431, 1232.

Table 1 (Cont'd)

Ex. No.	Het	Prep'n (Ref. Ex. No.)	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
79		B (69)	69	HCl salt 281-282	CD ₃ OD-CDCl ₃ 1.24(3H,t,J=7Hz), 3.11(6H,s), 3.51(2H,q,J=7Hz), 4.0(14H,m), 7.31(1H,s), 7.56(1H,s), 7.91(1H,s).	KBr tablet 3300, 3160, 1585, 1113, 995.
80		B (69)	90	HCl salt 249-250	DMSO-d ₆ -CDCl ₃ 0.815(6H,t,J=7Hz), 1.14(3H,t,J=6.5Hz), 1.51(4H,m), 3.36(6H,m), 3.91(14H,m), 7.0(1H,br.s), 7.58(1H,s), 7.75(1H,s), 7.81(1H,s), 8.8(2H,br.s), 12.4(1H,br.s).	KBr tablet 3408, 3116, 2952, 2916, 1580, 1487, 1430, 1230.

Example 81:

4-Amino-6,7,8-trimethoxy-2-(4-(5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidin-2-yl)-piperazino)quinazoline hydrochloride



5 In 20 ml of isoamyl alcohol as a solvent,
1.04 g of 4-amino-2-chloro-6,7,8-trimethoxyquinazoline
(synthesized by the process described in Japanese
Patent Laid-Open No. 7180/1971) and 1.0 g of the
5,6-dihydro-6-ethyl-5-oxo-2-piperazinopyrido[4,3-d]-
10 pyrimidine obtained in Referential Example 14 were
refluxed for 4 hours. After allowing the reaction
mixture to cool down, the precipitated crystals were
collected by filtration and then washed with methanol
to obtain 1.16 g of the above-identified compound
15 (yield: 61%).

Melting point: 241 - 242°C.

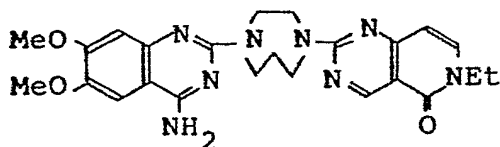
¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

1.23 (3H,t,J=7Hz), 3.96 (17H,m),
6.30 (1H,d,J=8Hz), 7.80 (1H,s),
20 7.85 (1H,d,J=8Hz), 9.12 (1H,s).

Example 82:

4-Amino-6,7-dimethoxy-2-(4-(5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidin-2-yl)-homopiperazino)quinazoline and its hydrochloride

5



In 20 ml of isoamyl alcohol as a solvent, were refluxed for 9 hours 0.81 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline, 0.88 g of the 5,6-dihydro-6-ethyl-5-oxo-2-homopiperazinopyrimido[4,3-d]pyrimidine
 10 obtained in Referential Example 14 and 0.48 g of tri-n-propylamine. After allowing the reaction mixture to cool down, 0.5 g of sodium hydrogencarbonate and 20 ml of water were added. After thoroughly stirring the resultant mixture, the solvent was distilled off. The
 15 residue was washed with water and then with hot methanol, thereby obtaining 1.24 g of the intended product (yield: 83%).

¹H-NMR spectrum (CDCl₃-DMSO-d₆ solution, δ ppm):

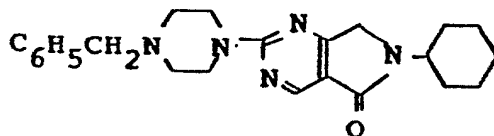
1.34 (3H,t,J=6Hz), 2.15 (2H,br.s), 3.93 (18H,m),
 20 6.30 (1H,d,J=7Hz), 7.20 (1H,s), 7.28 (1H,s),
 7.41 (1H,d,J=7Hz), 9.19 (1H,s).

The free base (1.24 g) obtained in the above preparation process was dissolved in methanol-dichloromethane, followed by an addition of 10 ml of HCl-saturated ethanol. Thereafter, excess hydrogen
5 chloride and solvent were distilled off to obtain 1.40 g of the hydrochloride of the above-identified compound.

Melting point: 236 - 238°C.

Referential Example 79:

10 2-(4-Benzylpiperazino)-6-cyclohexyl-5-oxo-
5,6-dihydro(7H)pyrrolo[3,4-d]pyrimidine



Dissolved in 40 ml of isoamyl alcohol was 2.0 g (5.34 mmol) of ethyl 2(4-benzylpiperazino)-4-chloromethylpyrimidine-5-carboxylate, followed by an addition
15 of 10.5 g (107 mmol) of cyclohexylamine. The resultant mixture was refluxed for 6 hours. After completion of the reaction, the solvent was distilled off and the residue was washed with ether to obtain 1.32 g of the above-identified compound as crystals (yield: 63%).

20 Melting point: 176 - 178°C.

Infrared absorption spectrum (CHCl_3 solution, cm^{-1}):

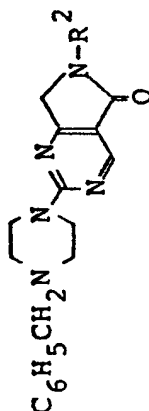
3120, 2850, 2800, 1670, 1610, 1572, 1350, 1005.


¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.20 - 2.00 (10H), 2.52 (4H,t,J=5Hz),
3.58 (2H,s), 3.96 (4H,t,J=5Hz), 4.18 (2H,s),
7.37 (5H,s), 8.69 (1H,s).

5 The compounds given in Table 2 were also
obtained in a similar manner.

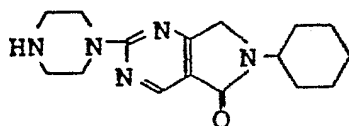
Table 2



R ²	Yield (%)	m.p. (°C)	¹ H-NMR spectrum (CDCl ₃ , δ ppm)	IR spectrum (KBr tablet, cm ⁻¹)
$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2\text{CH}_2\text{N} \\ \\ \text{CH}_3 \end{array}$	45	149-151	2.28(6H,s), 2.54(6H,m), 3.56(2H,s), 3.66(2H,t,J=6Hz), 3.96(4H,m), 4.35(2H,s), 7.36(5H,m), 8.67(1H,s).	2950, 2820, 1680, 1620, 1530, 1455.
-CH ₂ CH ₂ OCH ₃	46	97-98	2.51(4H,m), 3.36(3H,s), 3.56(2H,s), 3.66(4H,m), 3.95(4H,m), 4.36(2H,s), 7.35(5H,m), 8.68(1H,s).	2860, 1690, 1620, 1515, 1350.
-CH ₂ CH ₂ OH	62	160-161	2.52(4H,m), 3.15(1H,br.s), 3.58(2H,s), 3.73(2H,m), 3.96(6H,m), 4.36(2H,s), 7.38(5H,m), 8.66(1H,s).	3410, 2950, 2870, 1660, 1620, 1560, 1460.
-CH ₂ CH ₂ - 	59	162-164	2.52(4H,m), 2.97(2H,t,J=7Hz), 3.57(2H,s), 3.83(2H,t,J=7Hz), 3.94(4H,m), 4.03(2H,s), 7.34(10H,m), 8.68(1H,s).	2950, 1680, 1620, 1510, 1350.
-(CH ₂) ₆ CH ₃	46	135-137	0.88-1.6(11H,m), 2.52(4H,m), 3.58(4H,m), 3.96(4H,m), 4.20(2H,s), 7.37(5H,m), 8.68(1H,s).	2930, 1680, 1620, 1518, 1350, 1110.

Referential Example 80:

6-Cyclohexyl-5-oxo-2-piperazino-5,6-
dihydro(7H)pyrrolo[3,4-d]pyrimidine



Dissolved in 30 ml of ethanol was 1.2 g (3.07
5 mmol, Referential Example 79) of 2-(4-benzyl-
piperazino)-6-cyclohexyl-5-oxo-5,6-dihydro(7H)pyrrolo-
[3,4-d]pyrimidine, followed by an addition of 0.16 g of
10% Pd-C. The pyrimidine derivative was hydrogenated
at 60°C. After completion of the reaction, Pd-C was
10 filtered off and ethanol was distilled off to obtain
0.92 g of the above-identified compound as crystals
(yield: about 100%).

Melting point: 177 - 180°C.

Infrared absorption spectrum (CHCl_3 solution, cm^{-1}):

15 3330, 2920, 2850, 1670, 1610, 1570, 1345, 978.

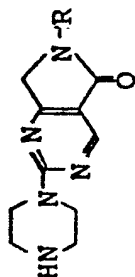
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.20 - 2.00 (10H), 2.94 (4H, t, $J=5\text{Hz}$),

3.92 (4H, t, $J=5\text{Hz}$), 4.19 (2H, s), 8.69 (1H, s).

The compounds given in Table 3 were also
20 obtained in a similar manner.

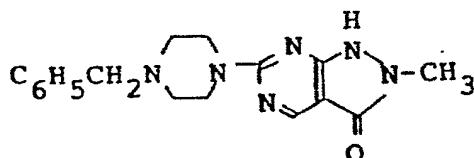
Table 3



R	Yield (%)	m.p. (°C)	¹ H-NMR spectrum (CDCl ₃ , δ ppm)	IR spectrum -1 (KBr tablet, cm ⁻¹)
$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2\text{CH}_2\text{N}- \\ \\ \text{CH}_3 \end{array}$	88	166-167	1.80(1H, br.s), 2.28(6H, s), 2.54 (2H, t, J=6Hz), 2.94(4H, m), 3.66(2H, t, J=6Hz), 3.92(4H, m), 4.35(2H, s), 8.68(1H, s).	3220, 2930, 2825, 1670, 1618, 1530.
$-\text{CH}_2\text{CH}_2\text{OCH}_3$	99	113-115	2.98(4H, m), 3.40(3H, s), 3.66(4H, m), 3.97(4H, m), 4.21(2H, s), 8.72(1H, s).	3250, 2940, 1680, 1620, 1530, 1430.
$-\text{CH}_2\text{CH}_2\text{OH}$	94	152-154	2.32(2H, br.s), 2.96(4H, m), 3.72(2H, m), 3.94(6H, m), 4.39(2H, s), 8.69(1H, s).	3380, 3320, 1660, 1620, 1520, 1355.
$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$	97	168-170	1.72(1H, br.s), 2.99(6H, m), 3.91(6H, m), 4.03(2H, s), 7.30(5H, m), 8.69(1H, s).	3300, 2900, 1670, 1618, 1530, 1230.
$-(\text{CH}_2)_6\text{CH}_3$	86	265-270 (dec'd)	0.88-1.6(11H, m), 2.96(6H, m), 3.55(2H, m), 3.94(4H, m), 4.21(2H, s), 8.69(1H, s).	2930, 1685, 1620, 1570, 1525, 1355.

Referential Example 81:

6-(4-Benzylpiperazino)-2-methyl-3-oxo-2,3-
dihydro-1H-pyrazolo[3,4-d]pyrimidine



Added at room temperature (about 20°C) to an
5 EtOH solution (20 ml) of 2.0 g of 2-methylhydrazine
was a chloroform solution (12 ml) of 5.3 g of the
ethyl 2-(4-benzylpiperazino)-4-chloropyrimidine-5-
carboxylate synthesized in Referential Example 63. The
resultant mixture was stirred for 3 hours. The solvent
10 was distilled off and ethyl acetate was added to the
resultant solid. After thoroughly mixing the thus-
obtained mixture, 3 g of crystals were collected by
filtration (yield: 63%).

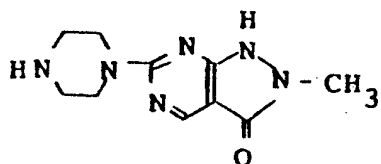
Melting point: 210 - 212°C.

15 ¹H-NMR spectrum (CDCl₃ solution, δ ppm):

2.55 (4H,m), 3.60 (5H,s), 3.96 (4H,m),
6.98 (1H,br.s), 7.36 (5H,m), 8.72 (1H,s).

Referential Example 82:

6-Piperazino-2-methyl-3-oxo-2,3-dihydro-1H-
20 pyrazolo[3,4-d]pyrimidine



A catalytic amount of 10% Pd-C was added to an EtOH solution (30 ml) of 3.0 g of 6-benzylpiperazino-2-methyl-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidine. In a hydrogen atmosphere, the resultant mixture was stirred at 60°C for 3 hours. After allowing the reaction mixture to cool down, the catalyst was filtered off and the filtrate was concentrated to obtain 1.8 g of the above-identified compound as yellowish crystals (yield: 88%).

Melting point: 272 - 276°C (decomposed).

¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

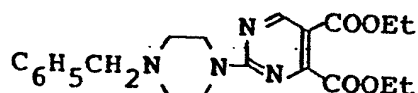
3.20 (4H,m), 3.64 (3H,s), 4.24 (2H,m),
8.70 (1H,s).

Infrared absorption spectrum (KBr tablet, cm⁻¹):

3600 - 3300, 1700, 1621, 1565, 1443.

Referential Example 83:

Diethyl 2-(4-benzylpiperazino)-4,5-pyrimidinedicarboxylate



To absolute ethanol with 0.91 g of sodium dissolved therein, 11.5 g of 1-amidino-4-benzyl-piperazine sulfate was added. The resultant mixture was stirred at room temperature for 30 minutes, to
5 which 8.8 g of ethyl ethoxymethyleneoxaloacetate [synthesized by the process described in J. Am. Chem. Soc., 73, 3684 (1951)] was added. After allowing them to react at room temperature for 2 days, the reaction was caused to proceed further for 1 hour while
10 heating the reaction mixture under reflux. After cooling the reaction mixture to room temperature, ethanol was distilled off under reduced pressure and the residue was dissolved in a mixture of water and ethyl acetate. After separation of the water layer,
15 the ethyl acetate layer was washed with water and then with saturated saline. After drying the ethyl acetate layer with magnesium sulfate, ethyl acetate was distilled off under reduced pressure to obtain 13.7 g of the above-identified compound as light brown
20 crystals (yield: 96%).

Melting point: 66°C.

Infrared absorption spectrum (nujol, cm^{-1}):

1750, 1715, 1590.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

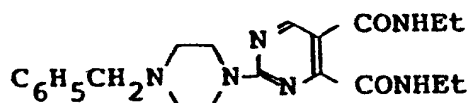
25 1.32 (3H,t,J=7Hz), 1.39 (3H,t,J=7Hz),
 2.49 (4H,t,J=5Hz), 3.54 (2H,s),

3.94 (4H,t,J=5Hz), 4.30 (2H,q,J=7Hz),
4.42 (2H,q,J=7Hz), 7.31 (5H,s), 8.85 (1H,s).

Referential Example 84:

5

N,N'-Diethyl-2-(4-benzylpiperazino)-4,5-
pyrimidinedicarboxylic acid amide



Charged in an autoclave were 1.5 g of the
diethyl 2-(4-benzylpiperazino)-4,5-pyrimidine-
dicarboxylate synthesized in Referential Example 83, 1
ml of ethylamine and 20 ml of DMF. They were reacted
10 at 150°C for 1 hour. After the reaction, DMF was
distilled off and the residue was added with 20 ml of
hexane and 5 ml of ethyl acetate. The resultant light
yellowish crystals of the above-identified compound
were collected by filtration [yield: 0.8 g (54%)].
15 Melting point: 201°C.

Infrared absorption spectrum (nujol, cm^{-1}):

3290, 1650, 1635, 1585.

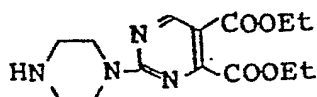
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.23 (3H,t,J=7Hz), 1.24 (3H,t,J=7Hz),
20 2.54 (4H,t,J=5Hz), 3.46 (2H,q,J=7Hz),
3.49 (2H,q,J=7Hz), 3.56 (2H,s),
3.89 (4H,t,J=5Hz), 7.32 (5H,s), 7.6 (1H,br.s),

9.16 (1H,s), 9.5 (1H,br.s).

Referential Example 85:

Diethyl 2-piperazino-4,5-pyrimidine-
dicarboxylate



5 The diethyl 2-(4-benzylpiperazino)-4,5-pyrimidinedicarboxylate (1.5 g) synthesized in Referential Example 83 was dissolved in a mixture of 20 ml of ethanol and 5 ml of acetic acid, followed by an addition of 0.15 g of 10% Pd-C. The resultant mixture
10 was stirred at 70°C for 1 hour in a hydrogen atmosphere. After the reaction, ethanol and acetic acid were distilled off under reduced pressure and the residue was dissolved in dichloromethane. The dichloromethane solution was washed with a saturated
15 aqueous solution of sodium bicarbonate. Dichloromethane was distilled off under reduced pressure to obtain 0.97 g of the above-identified compound as a yellowish oily product (yield: 81%).

Infrared absorption spectrum (neat, cm^{-1}):

20 2980, 1745, 1715, 1590, 1540, 1290, 1250.

^1H -NMR spectrum (CDCl_3 solution, δ ppm):

1.33 (3H,t,J=7Hz), 1.40 (3H,t,J=7Hz),

2.03 (1H, br.s), 2.92 (4H,t,J=5Hz),
4.31 (2H,t,J=7Hz), 4.43 (2H,t,J=7Hz),
8.87 (1H,s).

Referential Example 86:

5 N,N'-Diethyl-2-piperazino-4,5-pyrimidine-
 dicarboxylic acid amide



Dissolved in 30 ml of ethanol was 0.8 g of the
N,N'-diethyl-2-(4-benzylpiperazino)-4,5-pyrimidine-
dicarboxylic acid amide synthesized in Referential
10 Example 84, followed by an addition of 0.08 g of 10%
Pd-C. The resultant mixture was stirred at 60°C for 4
hours in a hydrogen atmosphere. After filtering off
the 10% Pd-C, ethanol was distilled off under reduced
pressure to obtain the above-identified compound as
15 light yellowish crystals [yield: 0.55 g (89%)].
Melting point: 73°C.

Infrared absorption spectrum (KBr tablet, cm^{-1}):

3300, 1640, 1585, 1520, 1450, 1265.

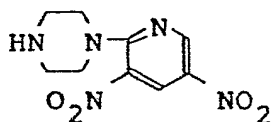
^1H -NMR spectrum (CDCl_3 solution, δ ppm):

20 1.24 (3H,t,J=7Hz), 1.26 (3H,t,J=7Hz),
 1.76 (1H, br.s), 2.94 (4H,t,J=5Hz),
 3.42 (2H,dt,J=7Hz,2Hz), 3.49 (2H,dt,J=7Hz,2Hz),

3.86 (4H,t,J=5Hz), 7.6 (1H,br.s), 9.16 (1H,s),
9.5 (1H,br.s).

Referential Example 87:

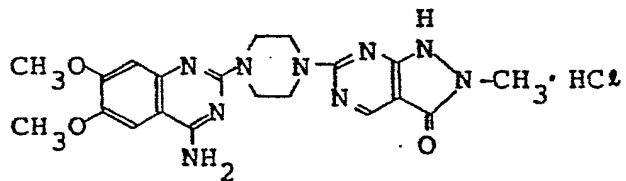
3,5-Dinitro-2-piperazinopyridine



5 In n-butanol (20 ml), 1 g of 2-chloro-3,5-dinitropyridine and 2.1 g of anhydrous piperazine were refluxed for 2 hours. Thereafter, n-butanol was distilled off under reduced pressure, followed by extraction with 2N-NaOH and chloroform. The chloroform
10 layer was washed with saturated saline and then dried with anhydrous magnesium sulfate. Under reduced pressure, chloroform was distilled off to obtain 0.4 g of the intended product (yield: 32%).

Example 83:

15 4-Amino-6,7-dimethoxy-2-(4-(2-methyl-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6-yl)piperazino)quinazoline hydrochloride



Refluxed for 5 hours in isoamyl alcohol

(30 ml) were 1.74 g (7.3 mmol) of 4-amino-2-chloro-6,7-dimethoxyquinazoline and 1.60 g (7.3 mmol) of the 6-piperazino-2-methyl-3-oxo-2,3-dihydro-1H-pyrazolo-[3,4-d]pyrimidine synthesized in Referential Example 82. After allowing the reaction mixture to cool down, the resultant crystals were collected by filtration and then washed with ethanol. The thus-obtained crude crystals were added with ethanol and refluxed for 2 hours. After allowing the mixture to cool down, crystals were collected by filtration and then dried to obtain 2.90 g of the above-identified compound (yield: 84%).

Melting point: 272 - 276°C (decomposed).

Infrared absorption spectrum (KBr tablet, cm^{-1}):

3400, 3180, 1655, 1594, 1530, 1495, 1438, 1257, 1112, 985.

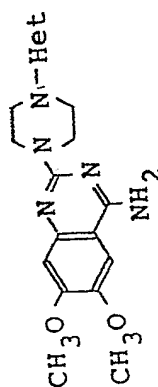
^1H -NMR spectrum (DMSO- d_6 solution, δ ppm):

3.64 (3H,s), 3.90 (3H,s), 3.94 (3H,s), 4.05 (8H,m), 7.64 (1H,s), 7.70 (1H,br.s), 7.82 (1H,s), 8.76 (1H,br.s), 8.82 (1H,s), 8.98 (1H,br.s), 12.50 (1H,br.s).

Examples 84 to 93:

Following the procedure of Example 83, the compounds given in Table 4 were obtained by using the piperazinopyrimidine derivatives obtained in their corresponding Referential Examples or the like.

Table 4



Ex. No.	Het	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
84		90	HCl salt 291 (dec'd)	DMSO-d ₆ 1.27(3H, t, J=7Hz), 1.31(3H, t, J=7Hz), 3.86(3H, s), 3.90(3H, s), 4.03(8H, br. s), 4.27(2H, q, J=7Hz), 4.35(2H, q, J=7Hz), 7.56(1H, s), 7.76(1H, s), 8.7(1H, br. s), 8.92(1H, s), 9.0(1H, br. s).	nujol 3160, 1720, 1715, 1665, 1640, 1605, 1590, 1535.
		58	HCl salt 298 (dec'd)	DMSO-d ₆ 1.09(3H, t, J=7Hz), 1.12(3H, t, J=7Hz), 3.29(4H, q, J=7Hz), 3.85(3H, s), 3.90 (3H, s), 4.00(8H, br. s), 7.52(1H, s), 7.74(1H, s), 8.25(1H, br. s), 8.59(1H, s), 8.7(3H, br. s).	nujol 3270, 3200, 1650, 1585, 1500, 1255.

Table 4 (Cont'd)

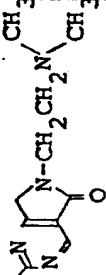
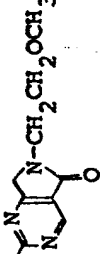
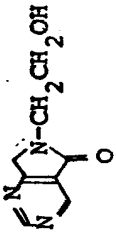
Ex. No.	Het	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
86		50	HCl salt 296-298 (dec'd)	CD ₃ OD-CDCl ₃ 2.68(6H,s), 3.06(2H,t, J=6Hz), 3.86(2H,t, J=6Hz), 3.98(3H,s), 4.02(3H,s), 3.06(8H,m), 4.46(2H,s), 7.25(1H,s), 7.54(1H,s), 8.74(1H,s).	KBr tablet 3340, 1650, 1613, 1580, 1435, 1240.
87		35	HCl salt 254-256	CD ₃ OD-CDCl ₃ 3.40(3H,s), 3.72(4H,m), 3.99(3H,s), 4.40(3H,s), 4.12(8H,m), 4.50(2H,s), 7.28(1H,s), 7.62(1H,s), 8.74(1H,s).	KBr tablet 3400, 1660, 1590, 1258.
88		90	HCl salt 282-283 (dec'd)	DMSO-d ₆ 3.58(4H,m), 3.88(3H,s), 3.92(3H,s), 4.04(8H,m), 4.48(2H,m), 7.58(1H,s), 7.79(1H,s), 8.72(1H,s).	KBr tablet 3320, 1660, 1612, 1590, 1433, 1259.

Table 4 (Cont'd)

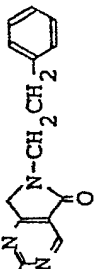
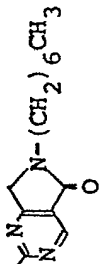
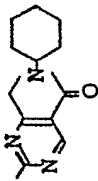
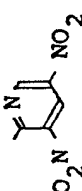
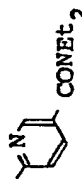
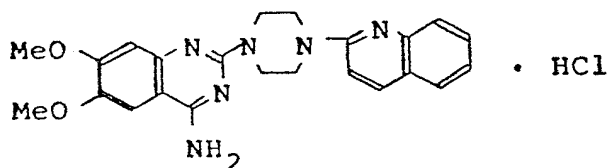
Ex. No.	Het	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
89		57	HCl salt 270-270.8	CD ₃ OD-CDCl ₃ 3.00(2H,t,J=7Hz), 3.86(2H,t,J=7Hz), 3.98(3H,s), 4.03(3H,s), 4.06(8H,m), 4.18(2H,s), 7.22(1H,s), 7.28(5H,m), 7.61(1H,s), 8.71(1H,s).	KBr tablet 3320, 1650, 1590, 1430, 1255.
90		57	HCl salt 257.6-258.4	CD ₃ OD-CDCl ₃ 0.90-1.7(13H,m), 3.6(2H,t,J=7H), 3.99(3H,s), 4.05(3H,s), 4.10(8H,m), 4.39(2H,s), 7.30(1H,s), 7.61(1H,s), 8.73(1H,s).	KBr tablet 3400, 1650, 1590, 1430, 1255.
91		55	HCl salt 252-254	DMSO-d ₆ 1.00-2.2(10H), 3.5(1H,m), 3.88(3H, s), 3.92(3H,s), 4.07(8H,s), 4.38(2H, s), 7.67(1H,s), 7.81(1H,s), 8.71(1H, s), 9.00(2H,br.d).	KBr tablet 3340, 1655, 1613, 1595, 1520, 1260.

Table 4 (Cont'd)

Ex. No.	Het	Yield (%)	Isolated form (m.p. °C)	¹ H-NMR spectrum, δppm	IR spectrum (cm ⁻¹)
92		62	HCl salt 281-291	DMSO-d ₆ 3.86(3H,s), 3.89(3H,s), 3.98(8H,m), 7.48(1H,s), 7.75(1H,s), 8.92(1H,d, J=2Hz), 9.22(1H,d,J=2Hz).	KBr tablet 3080, 1645, 1588, 1328, 1108.
93		38	HCl salt >300	DMSO-d ₆ 1.16(6H,t,J=7Hz), 3.24-3.56(12H,m), 3.89(3H,s), 3.92(2H,s), 6.90(1H,d, J=9Hz), 7.52-7.70(2H,m), 7.75(1H,s), 8.18(1H,d,J=2Hz), 8.60(1H,br.s), 8.90(1H,br.s).	KBr tablet 3350, 3120, 2900, 1652, 1590, 1242, 1110, 985, 765.

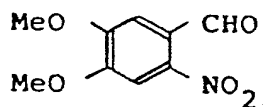
Example 94:4-Amino-6,7-dimethoxy-2-(4-(2-quinolylyl)-piperazino)quinazoline hydrochloride

Mixed were 0.72 g (2.5 mmol) of 4-amino-6,7-dimethoxy-2-piperazinoquinazoline, 0.63 g (3.9 mmol) of 2-chloroquinoline, 0.43 g (3 mmol) of tri-n-propylamine and 15 ml of isoamyl alcohol. The mixture was refluxed for 16 hours. After cooling the reaction mixture, the resultant crystals were collected by filtration, followed by their dissolution in a mixed solvent of 10 ml of dichloromethane and 10 ml of methanol. To the solution, 2 ml of a 20% ethanol solution of hydrochloric acid was added. The solvents were distilled off to obtain 0.90 g of the above-identified compound (yield: 80%).

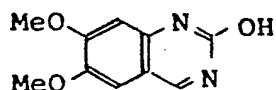
Melting point: 243.5 - 244.5°C.

¹H-NMR spectrum (DMSO-d₆ solution, δ ppm):

3.87 (3H,s), 3.91 (3H,s), 3.7 - 4.1 (8H,br.s),
6.8 - 8.1 (8H,m).

Referential Example 88:4,5-Dimethoxy-2-nitrobenzaldehyde

After reacting 135 g of 3,4-dimethoxybenz-
aldehyde and 500 ml of conc. nitric acid at 10°C for
5 20 hours, the reaction mixture was poured in 3 l of
ice water and the resultant crystals were collected by
filtration. The crystals were dissolved in a mixed
solvent of 8 l of toluene and 500 ml of ethyl
acetate. After washing the resultant solution once
10 with a saturated aqueous solution of sodium
bicarbonate, three times with water and then once with
saturated saline, the solution was concentrated to
about 500 ml under reduced pressure. The concentrate
was cooled to room temperature and the resultant
15 yellowish crystals (77.71 g) were then collected by
filtration (yield: 61%).

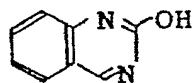
Referential Example 89:6,7-Dimethoxy-2-hydroxyquinazoline

Dissolved in a mixed solvent of 30 ml of dichloromethane and 30 ml of methanol were 3.17 g of the 4,5-dimethoxy-2-nitrobenzaldehyde synthesized in Referential Example 88, followed by an addition of
5 0.16 g of 5% Pd-C. The resultant mixture was stirred for 4 hours in a hydrogen atmosphere. Pd-C was filtered off and the solvent was distilled off under reduced pressure. The residue was dissolved in 30 ml of acetic acid, followed by an addition of potassium
10 cyanate. After reacting the contents overnight at room temperature, they were heated and reacted for further 1 hour under reflux. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography (silica gel; eluent: 5:1 mixed solvent
15 of dichloromethane and MeOH), thereby obtaining 1.51 g of the above-identified compound as colorless crystals (yield: 49%).

Melting point: 260 - 263°C.

Referential Example 90:

20 2-Hydroxyquinazoline



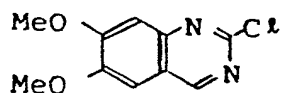
Following the procedure of Referential Example 89, the above-identified compound was obtained from o-

nitrobenzaldehyde.

Melting point: 189°C.

Referential Example 91:

2-Chloro-6,7-dimethoxyquinazoline

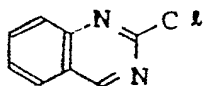


5 Phosphorus oxychloride (50 ml) was added to
5.0 g of the 6,7-dimethoxy-2-hydroxyquinazoline
synthesized in Referential Example 89. They were
heated and reacted for 8 hours under reflux. After
allowing the reaction mixture to cool down, phosphorus
10 oxychloride was distilled off under reduced pressure
and the residue was dissolved in dichloromethane.
After washing the dichloromethane solution once with a
saturated aqueous solution of sodium bicarbonate, once
with water and then once with saturated saline, the
15 solution was dried with anhydrous sodium sulfate. The
solvent was distilled under reduced pressure and the
residue was purified by column chromatography (silica
gel; eluent: 50:1 mixed solvent of dichloromethane and
methanol), thereby obtaining 2.1 g of the intended
20 product as crystals (yield: 38%).

Melting point: 237.- 238°C.

Referential Example 92:

2-Chloroquinazoline



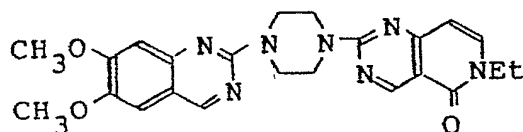
Following the procedure of Referential Example 91, the above-identified compound was obtained from 2-hydroxyquinazoline.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

7.72 (1H,m), 7.96 (3H,m), 9.32 (1H,s).

Example 95:

6,7-Dimethoxy-2-(4-(5,6-dihydro-6-ethyl-5-oxopyrido[4,3-d]pyrimidine-2-yl)piperazino)-quinazoline



Tri-n-propylamine (0.43 g) was added to 0.67 g of the 2-chloro-6,7-dimethoxyquinazoline synthesized in Referential Example 91 and 0.78 g of the 6-ethyl-2-piperazinopyrido[4,3-d]pyrimidine-5(6H)-one synthesized in Referential Example 14. Using 5 g of isoamyl alcohol as a solvent, they were heated and reacted for 10 hours under reflux. The resultant crystals were

collected by filtration and then washed first with ethyl acetate and then with hexane. They were dried to obtain 1.24 g of the above-identified compound as white crystals (yield: 92%).

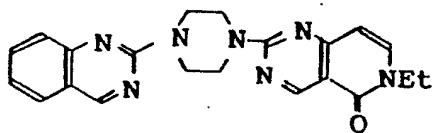
5 Melting point: 259 - 262°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.36 (3H,t,J=7Hz), 3.96 (3H,s),
3.97 (2H,q,J=7Hz), 4.02 (3H,s),
4.05 (8H,br.s), 6.32 (1H,d,J=7Hz), 6.93 (1H,s),
10 6.98 (1H,s), 7.30 (1H,d,J=7Hz), 8.82 (1H,s),
9.28 (1H,s).

Example 96:

2-(4-(5,6-Dihydro-6-ethyl-5-oxopyrido[4,3-d]-
pyrimidine-2-yl)piperazino)quinazoline



15 In a manner similar to that employed in Example 95, the above-identified compound was obtained from the 2-chloroquinazoline synthesized in Referential Example 95 and the 6-ethyl-2-piperazinopyrido[4,3-d]-pyrimidine-5(6H)-one synthesized in Referential Example
20 14 (yield: 30%).

Melting point: 222 - 224°C.

¹H-NMR spectrum (CDCl₃ solution, δ ppm):

1.33 (3H,t,J=7Hz), 3.92 (2H,q,J=7Hz),
4.08 (8H,br.s), 6.30 (1H,d,J=7Hz),
7.22 (1H,d,J=7Hz), 7.24 (2H,m), 7.62 (2H,m),
9.0 (1H,s), 9.27 (1H,s).

5 Each of the following Examples, which are
directed to preparations, makes use of one of the
compounds described in Examples 1 to 96 or one of other
pharmaceutical compounds embraced by the general
formula [I] as an active component.

10 Example 97:

Tablets containing 0.2 mg of their respective
active components were individually prepared in the
following manner.

		<u>per tablet</u>
15	Active component	0.2 mg
	Starch	54.8 mg
	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone (as 10% aqueous solution)	4 mg
20	Calcium carboxymethylcellulose	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	1.0 mg
		<hr/> (Total) 100 mg

25 The active component, starch and microcry-
stalline were caused to pass through an 80-mesh sieve
to mix them intimately. The thus-obtained powder was
added with the polyvinylpyrrolidone solution, followed

by granulation. The resultant granules were classified through an 18-mesh sieve. The thus-prepared granules were dried at 50 - 60°C and again classified through an 18-mesh sieve. The granules were then added with
5 the calcium carboxymethylcellulose, magnesium stearate and talc which had in advance been classified through an 80-mesh sieve individually. After mixing them together, the resultant mixture was formed into tablets, each having a weight of 100 mg, by a tableting
10 machine.

Example 98:

Tablets containing 1 mg of their respective active components were individually prepared in the following manner.

15		<u>per tablet</u>
	Active component	1 mg
	Starch	60 mg
	Microcrystalline cellulose	35 mg
	Light silicic anhydride	3 mg
20	Magnesium stearate	1 mg
		<hr/>
		(Total) 100 mg

The above components were caused to pass through an 80-mesh sieve, thereby mixing them intimately. The thus-obtained powder was compression-formed to prepare
25 tablets each of which had a weight of 100 mg.

Example 99:

Capsules containing 0.5 mg of their respective active components were individually prepared in the following manner.

5		<u>per capsule</u>
	Active component	0.5 mg
	Dry starch	50 mg
	Microcrystalline cellulose	47.5 mg
	Magnesium stearate	2 mg
10		(Total) 100 mg

The above components were mixed and then caused to pass through an 80-mesh sieve, thereby mixing them intimately. The thus-obtained powder was filled 100 mg by 100 mg in capsules.

15 Example 100:

Ten parts of ammonium polyacrylate were dissolved in 60 parts of water. On the side, 2 parts of glycerin diglycidylether were dissolved with heating in 10 parts of water. Still on the side, 10 parts of polyethylene glycol (Grade 400), 10 parts of water and 0.1 part of an active component were stirred to dissolve the active component. While stirring the aqueous solution of ammonium polyacrylate, the aqueous solution of glycerin diglycidylether and the aqueous solution, which contained polyethylene glycol and the active component, was added to and mixed with the

aqueous solution of ammonium polyacrylate to prepare a drug-containing water-base gel formulation. The gel formulation was then coated on a flexible plastic film to give a coat weight of 0.05 mg per square centimeters in term of the active component. The surface was covered by a release paper web, followed by cutting same into cataplasms, each, of 35 cm² wide.

Example 101:

Prepared was a mixed water-base sol formulation of 100 parts of sodium polyacrylate, 100 parts of glycerin, 150 parts of water, 0.2 part of triepoxy-propyl isocyanurate, 100 parts of ethanol, 25 parts of isopropyl myristate, 25 parts of propylene glycol and 1 part of an active component. The sol formulation was then coated on the surface of a nonwoven rayon fabric of a composite film, which was composed of the nonwoven rayon fabric and a polyethylene film, to 100 µm thick so that a drug-containing tacky mass layer was formed. The content of the releasing adjuvants (i.e., isopropyl myristate and propylene glycol) in the layer was about 20 wt.%. Thereafter, the tacky mass layer was cross-linked at 25°C for 24 hours. A release film was applied on the surface of the tacky mass layer, followed by cutting same into cataplasms, each, of 35 cm² wide.

Example 102:

Mixed at 70°C in a kneader was a composition which consisted of 110 parts of a styrene-isoprene-styrene block copolymer, 90 parts of a terpene resin, 5 60 parts of olive oil, 0.1 part of ethylene glycol diacrylate and 0.5 part of an active component.

From an extruder, the mixture was then extruded and coated at 60°C onto one side of a polyvinyl chloride film of 100 µm thick to a thickness of 100 µm, 10 thereby forming a drug-containing tacky mass layer. Thereafter, the tacky mass layer was exposed to ionizing radiation to give a dose of 10 Mrad. The thus-exposed layer was brought into a contiguous relation with a release film, followed by cutting same 15 into desired sizes to form cataplasms.

[Effects of the Present Invention]

The present invention has made it clear through zoopery that as mentioned above, the compounds [I] of this invention have extremely strong and long-acting 20 antihypertensive effects and some of the compounds reduce or substantially avoid orthostatic hypotension, which is an undesirable side effect accompanying short-term blood pressure drop, compared with the conventionally-known compounds. The antihypertensive 25 effects of certain compounds of this invention as well as their antihypertensive effects along the passage of

time, i.e., their antihypertensive patterns and long-acting properties were investigated on spontaneously hypertensive rats (SHRs). Investigation results are shown in Table 5. Many of the compounds of this invention showed stronger antihypertensive activity, weaker degrees of blood pressure drop upon an elapsed time of 1 hour after the administration of the drugs, and development of milder antihypertensive effects and longer-lasting patterns, all, compared with prazosin employed as Control. Furthermore, the toxicity levels of the compounds of this invention are generally weak. By way of example, their acute toxicity are shown in Table 6. As demonstrated herein, the compounds of this invention are generally believed to serve as drugs which have higher activity and lower toxicity, i.e., higher safety. Hereinafter, biological activities of certain compounds of this invention will be shown in Tests 1 and 2.

Test 1:

The antihypertensive effects of the certain compounds of this invention were studied in the following manner.

Among male, spontaneously hypertensive rats (SHRs) of 20 weeks of age or older and 350 - 430 g heavy all of which had developed hypertension, those having systolic blood pressures of 180 mmHg or higher

were used in groups, each of which was constituted of 3
- 4 of the rats. Blood pressures were measured
indirectly in terms of systolic blood pressures at tail
arteries by a hemodynamometer (W+W electronic, BP-8005)
5 under no anesthesia before administration of drugs and
upon elapsed time of 1, 3, 6 and 24 hours after the
administration. Besides, heart rates were also
measured simultaneously. The compounds were each
dissolved or suspended in a 0.5% methylcellulose
10 solution and then administered orally. Results are
shown in Table 5.

Table 5 Effects on Blood Pressures and Heart Rates of Spontaneously Hypertensive Rats

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in heart rate
	1 hour later	3 hours later	6 hours later	24 hours later	
1	-10.7	-17.3	-23.0	-8.2	+4.1
2	-9.0	-23.9	-38.8	-16.4	+18.4
3	-2.5	-8.0	-15.1	-5.0	+7.1
4	-4.4	-22.1	-26.5	-16.7	+5.7
5	0	-6.3	-13.2	-6.3	+2.6
6	-1.5	-13.8	-16.7	-9.9	+5.1
7	+1.5	-4.4	-9.3	-2.9	+2.8
8	-0.5	-9.5	-11.4	-4.0	+5.2
9	-1.5	-8.1	-9.6	-5.1	+4.3
10	+1.5	-14.4	-11.9	-5.0	+5.2
11	-0.5	-16.6	-17.1	-6.8	+5.7
12	-11.0	-14.3	-19.0	-6.7	+7.0

* All administered orally at a dosage of 1 mg/Kg except for the compounds of Examples 65 and 92 (10 mg/Kg).

** Each percent change in heart rate is indicated by the corresponding maximum value.

Table 5 (Cont'd)

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in heart rate
	1 hour later	3 hours later	6 hours later	24 hours later	
13	-1.0	-3.9	-10.6	-3.9	+7.4
14	-1.9	-4.8	-13.9	-11.0	+7.3
15	-2.9	-7.7	-12.0	-7.7	+3.7
16	-2.0	-8.9	-15.3	-8.9	+7.5
17	0	-20.2	-27.9	-12.0	+10.8
18	0	-3.9	-9.8	-3.9	+11.1
19	-2.4	-10.1	-11.1	-2.9	+2.9
20	+1.5	-12.5	-12.0	-2.0	+5.7
21	-17.2	-23.2	-23.6	-3.4	+7.4
22	-1.5	-10.1	-17.1	-4.0	+17.7
23	-11.7	-21.9	-27.0	-2.6	+23.1
24	-7.2	-24.8	-28.6	-8.7	+12.0
25	-4.3	-23.9	-35.4	-6.7	+12.9
26	-8.8	-15.2	-21.6	-4.9	+9.8
27	-5.4	-17.6	-21.0	-2.4	+8.3

Table 5 (Cont'd)

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in heart rate
	1 hour later	3 hours later	6 hours later	24 hours later	
28	-17.2	-15.3	-31.6	-3.3	+11.7
29	-5.2	-23.0	-35.2	-13.1	+10.1
30	-7.4	-24.7	-32.1	-8.8	+11.7
31	-2.8	-8.5	-17.8	-3.8	+14.5
32	-20.2	-30.5	-35.2	-16.4	+11.0
33	-20.4	-27.0	-32.1	-9.7	+17.5
34	+0.5	-9.1	-13.9	-7.2	+2.3
35	-0.5	-8.7	-16.3	-15.9	+9.1
36	-14.6	-16.5	-15.0	-2.4	+9.5
37	-4.7	-16.4	-21.1	-8.5	+5.8
38	-26.6	-24.1	-27.6	-7.9	+7.9
39	-4.4	-12.7	-7.3	+1.5	+2.2
40	-1.4	-15.9	-18.4	-8.2	+5.8
41	-11.2	-19.5	-25.9	-3.9	+9.2
42	-16.5	-19.5	-24.0	-7.5	+5.2
43	+4.5	+0.5	-6.5	-9.5	+5.7

Table 5 (Cont'd)

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in heart rate
	1 hour later	3 hours later	6 hours later	24 hours later	
44	+9.1	0	-4.0	0	+7.9
45	-1.5	-2.5	-8.0	-5.5	+4.2
46	0	-11.9	-17.5	-5.7	+7.4
47	-3.5	-9.0	-12.5	-2.5	+6.3
48	-4.5	-9.0	-15.0	-4.0	+6.9
49	-4.5	-10.6	-13.1	-7.5	+6.3
50	-1.5	-8.7	-14.6	-6.3	+2.9
51	+8.6	0	-4.1	-2.5	+3.0
52	-8.0	-13.0	-19.5	-3.0	+3.6
53	-27.9	-31.3	-36.1	-12.0	+25.7
54	-4.3	-11.4	-16.7	-4.8	+5.2
55	-6.5	-21.9	-29.9	-7.5	+7.0
56	-21.4	-22.4	-22.9	-4.5	+13.5
57	-10.4	-18.9	-27.9	-9.0	+4.3
58	-7.4	-17.6	-22.5	-9.8	+9.8

Table 5 (Cont'd)

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in pulse rate
	1 hour later	3 hours later	6 hours later	24 hours later	
59	-10.1	-23.9	-30.6	-12.4	+5.7
60	-1.6	-5.2	-8.8	-1.0	+6.0
61	-2.4	-22.0	-28.2	-12.0	+12.4
62	-1.4	-24.0	-31.3	-21.2	+7.6
63	+3.1	-4.7	-9.0	-6.6	+6.8
64	-1.4	-9.6	-13.9	-1.9	+9.9
65	-4.9	-18.4	-21.4	-6.3	+8.9
66	-18.0	-23.7	-28.9	-16.0	+3.8
67	-21.4	-28.6	-38.4	-16.7	+7.4
68	+1.4	-19.6	-28.2	-11.5	+5.2
69	-12.9	-22.7	-24.7	-4.6	+7.4
70	-7.8	-17.5	-23.3	-4.4	+13.7
71	+0.5	-13.4	-19.1	-9.6	+15.9
72	+2.9	-2.0	-2.5	-2.9	+8.6
73	-0.5	0	-7.0	-8.0	+4.3
74	-0.5	-14.1	-23.3	-12.1	+9.0

Table 5 (Cont'd)

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in pulse rate
	1 hour later	3 hours later	6 hours later	24 hours later	
75	+12.2	+0.5	-7.8	-3.9	+8.2
76	0	-3.8	-7.2	-9.6	+2.9
77	-31.0	-32.9	-36.2	-13.8	+25.1
78	-23.4	-33.7	-50.2	-18.5	+23.7
79	-27.9	-33.7	-45.2	-21.2	+22.3
80	-13.9	-26.0	-33.2	-10.1	+12.3
81	-0.5	-7.3	-12.1	-8.7	+3.8
82	+0.5	-6.9	-8.8	-6.4	+5.8
83	-3.9	-4.4	-5.3	-0.5	+5.6
84	+0.5	0	-1.5	-0.5	+2.2
85	-1.5	-7.3	-12.2	-3.9	+3.5
86	+0.5	0	-6.4	-0.5	+7.1
87	-6.9	-15.2	-21.6	-2.5	+17.7
88	+0.5	-4.4	-6.9	-2.0	+5.8
89	-2.4	-13.3	-13.8	-2.9	+5.8
90	+2.3	-6.8	-15.5	-2.7	+8.7

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Table 5 (Cont'd)

Compound* Example #	Antihypertensive effects, change (%) in blood pressure				Change (%)** in heart rate
	1 hour later	3 hours later	6 hours later	24 hours later	
91	-4.0	-8.0	-12.9	-2.5	+8.2
92	+1.4	-3.3	-9.4	-6.1	+8.5
93	-4.5	-9.0	-10.5	-5.0	+8.0
94	-0.5	-12.7	-22.1	-5.4	+5.4
95	+2.5	-2.9	-6.4	-3.9	+5.8
96	+3.0	-2.5	-8.0	-6.5	+2.9
Prazosin	-23.6	-25.1	-24.6	-5.0	+8.0
Terazosin	-22.4	-25.9	-23.4	-5.4	+7.2
E-643***	-4.8	-12.0	-13.5	-6.7	+8.8

*** "E-643" is Eisai's Bunazosin.

Test 2:

The acute toxicity of certain compounds of this invention were studied in the following manner.

Namely, male ddy-mice of 5 weeks of age and male
 5 Wister rats of 8 weeks of age were fasted for 18 hours
 and used in groups each of which was constituted of 4 -
 5 of the mice or rats. The compounds were each
 dissolved or suspended in a 0.5% methylcellulose
 solution and administered orally (P.O.). On the
 10 fourteenth day after the administration, their toxicity
 were judged. Results are shown in Table 6.

Table 6 Acute Toxicity for Mouse and Rat

Compound Ex. No.	Mouse		Rat	
	1 g/KgP.O.	3 g/KgP.O.	1 g/KgP.O.	3 g/KgP.O.
1	0/5	0/5	0/5	0/5
2	0/5	0/5	0/5	0/5
4	0/5	0/5	0/5	0/5
17	0/5	-	-	-
21	0/4	-	-	-
23	0/5	0/5	-	-
24	0/5	0/5	0/5	0/5
25	0/5	-	-	-
28	0/5	-	-	-
29	0/5	0/5	0/5	0/4
30	0/5	-	-	-
32	0/5	-	-	-
39	0/5	-	-	-

Table 6 (Cont'd)

Compound Ex. No.	Mouse		Rat	
	1 g/KgP.O.	3 g/KgP.O.	1 g/KgP.O.	3 g/KgP.O.
62	0/5	-	0/5	-
66	0/5	-	-	-
70	0/4	-	-	-
Prazosin	0/5	0/5	0/5	0/3
Terazosin	0/5	1/5	-	-
E-643*	0/5	-	2/4	-

Note: Each numeral set indicates the number of dead animals/the number of tested animals. Hyphens (-) indicate that no tests were effected.

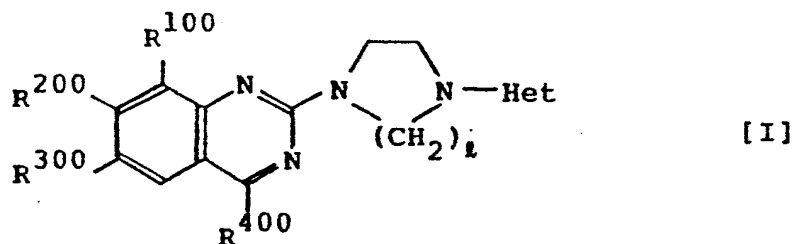
* "E-643" is Eisai's Bunazosin.

As shown in Table 5, the compounds of this invention exhibited sufficient antihypertensive effects when orally administered at the dosage of 1 mg/Kg. The development of their effects were gradual and their maximum effects were observed 6 hours after their administration or even later. In addition, their effects were observed even 24 hours after their administration. They are thus long-acting compounds. With respect to heart rate, the degrees of its increases were slight. From these results, many of the compounds of this invention are expected to show higher antihypertensive effects, to develop lower degrees of heart rate increases and to be less susceptible of developing orthostatic hypotension due to short-term

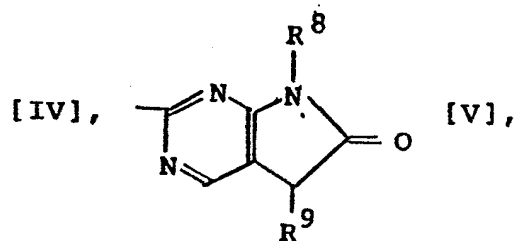
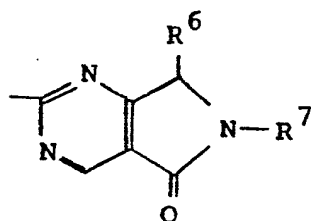
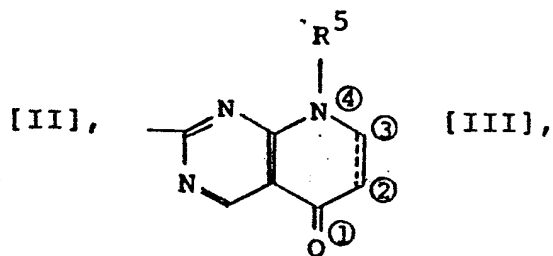
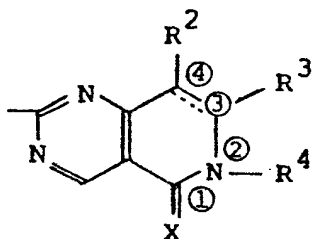
drop in blood pressure, all, compared with prazosin as Control. These features of the compounds of this invention are believed to make them excellent for the treatment of hypertension of mammals. Moreover, their acute toxicity are weak as shown in Table 6. In view of their amounts to be required to develop their efficacy as drugs, they are considered to be highly safe compounds.

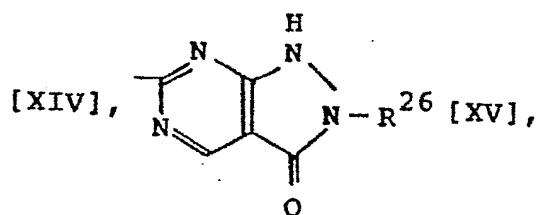
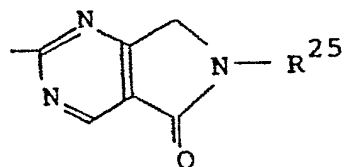
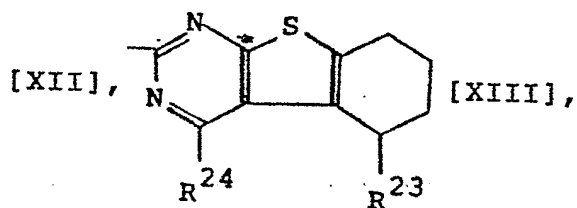
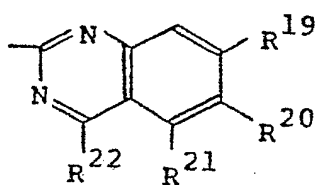
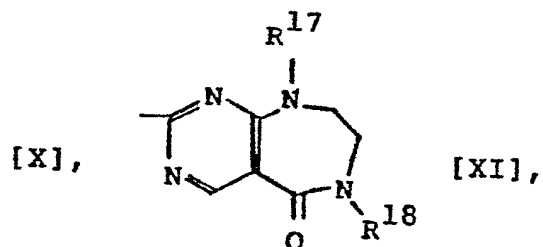
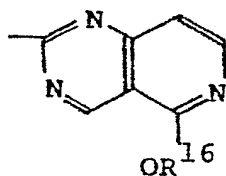
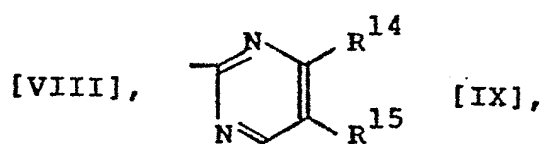
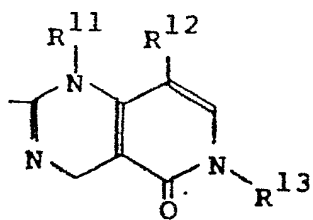
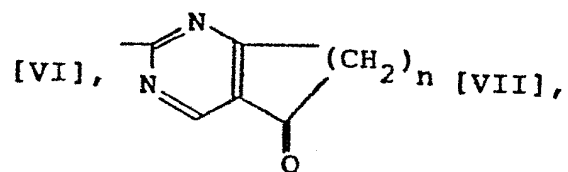
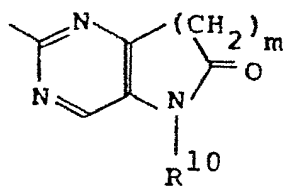
CLAIMS:

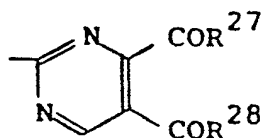
- 1 1. A quinazoline derivative represented by the
 2 following general formula [I] or a pharmacologically
 3 acceptable salt thereof:



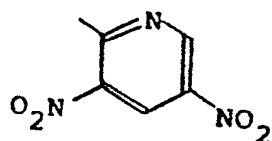
- 4 wherein R^{100} means a hydrogen atom or methoxy group,
 5 R^{200} and R^{300} denote individually a hydrogen atom
 6 or lower alkoxy group, R^{400} is a hydrogen atom or
 7 amino group, l stands for 2 or 3, and Het is
 8 represented by any one of the following formulae [II]
 9 through [XIX]:



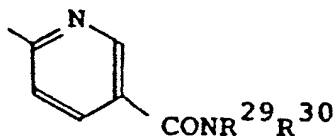




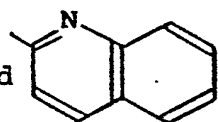
[XVI],



[XVII],



[XVIII], and



[XIX]

10 wherein,

11 in the formula [II], either single or double
 12 bond is formed between the 3- and 4-positions, R^2
 13 means a hydrogen atom or a lower alkyl, aralkyl, cyano
 14 or formyl group, R^3 denotes a hydrogen atom or a
 15 lower alkoxy-carbonyl or phenyl group, R^4 is a
 16 hydrogen atom or a lower alkyl, lower cycloalkyl,
 17 hydroxy-substituted lower alkyl, lower alkoxy-
 18 substituted lower alkyl, phenyl or aralkyl group, and X
 19 stands for an oxygen or sulfur atom,

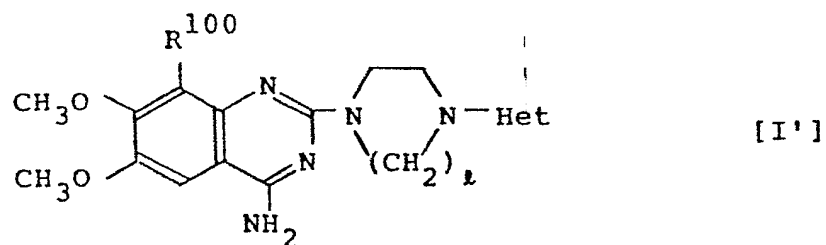
20 in the formula [III], either single or double
 21 bond is formed between the 2- and 3-positions, and R^5
 22 means a hydrogen atom or a lower alkyl group,

23 in the formula [IV], R^6 and R^7 mean
 24 individually a hydrogen atom or a lower alkyl group,

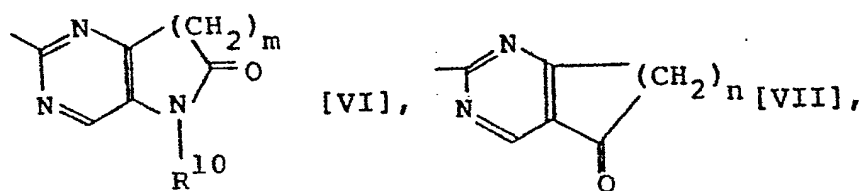
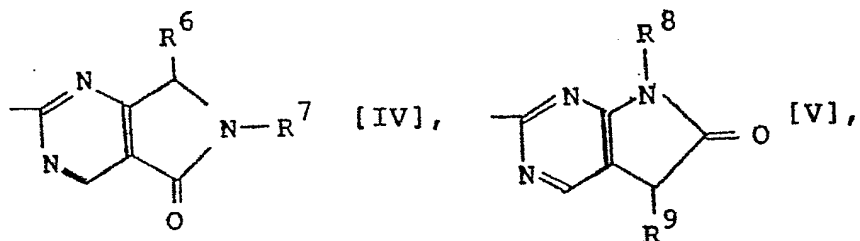
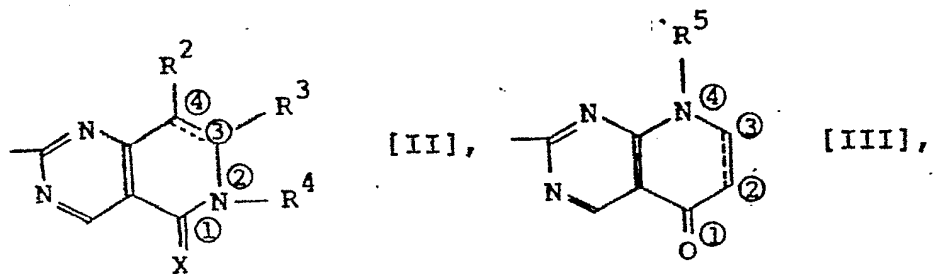
25 in the formula [V], R^8 and R^9 mean
26 individually a hydrogen atom or a lower alkyl group,
27 in the formula [VI], m stands for 2 or 3, and
28 R^{10} means a hydrogen atom or a lower alkyl group,
29 in the formula [VII], n stands for an integer of
30 from 2 to 4,
31 in the formula [VIII], R^{11} to R^{13} mean
32 individually a hydrogen atom or a lower alkyl group,
33 in the formula [IX], R^{14} means a hydrogen atom
34 or a hydroxyl, lower alkyl, $-NR^{31}R^{32}$ in which R^{31}
35 is a hydrogen atom or a lower alkyl group and R^{32} is
36 a hydrogen atom or a lower alkyl or lower acyl group,
37 lower alkylthio or lower alkoxy group, R^{15} denotes a
38 lower acyl, lower alkoxycarbonyl, $-CONR^{33}R^{34}$ in
39 which R^{33} is a hydrogen atom or a lower alkyl group,
40 R^{34} is a hydrogen atom or a lower alkyl, phenyl,
41 aralkyl, halogen-substituted lower alkyl or cycloalkyl
42 group or R^{33} and R^{34} couples together to form a
43 methylene moiety which in turn forms a ring having 4 to
44 5 carbon atoms together with the associated nitrogen
45 atom, $-CONHNR^{35}R^{36}$ in which R^{35} and R^{36} are
46 individually a lower alkyl group, $-CH_2CONHR^{37}$ in
47 which R^{37} is a lower alkyl, or cyano group,
48 in the formula [X], R^{16} means a lower alkyl
49 group,

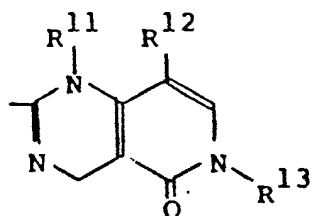
50 in the formula [XI], R^{17} and R^{18} mean
51 individually a hydrogen atom or a lower alkyl group,
52 in the formula [XII], R^{19} through R^{21} means
53 a hydrogen atom or a lower alkoxy group, and R^{22}
54 denotes $-NR^{38}R^{39}$ in which R^{38} and R^{39} are
55 individually a hydrogen atom or a lower alkyl group, or
56 a hydrogen atom,
57 in the formula [XIII], R^{23} means a hydrogen
58 atom or a lower alkyl group, and R^{24} denotes a
59 hydrogen atom or a lower alkylthio group,
60 in the formula [XIV], R^{25} means an alkyl,
61 cycloalkyl, hydroxy-substituted lower alkyl group,
62 lower alkoxy-substituted lower alkyl, di(lower
63 alkylamino)-substituted lower alkyl or aralkyl group,
64 in the formula [XV], R^{26} means a lower alkyl
65 group,
66 in the formula [XVI], R^{27} and R^{28} are either
67 same or different and mean individually a lower alkoxy,
68 hydroxyl or lower alkylamino group, or R^{27} and R^{28}
69 couples together to form a lower alkyl-substituted
70 imino group, and
71 in the formula [XVIII], R^{29} and R^{30} are
72 either same or different and mean individually a lower
73 alkyl group.

- 1 2. A quinazoline derivative represented by the
 2 following general formula [I'] or a pharmacologically
 3 acceptable salt thereof:

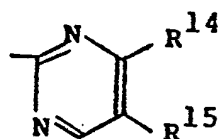


- 4 wherein R^{100} means a hydrogen atom or a methoxy
 5 group, l stands for 2 or 3, and Het is represented by
 6 any one of the following formulae [II] through [XIII]:

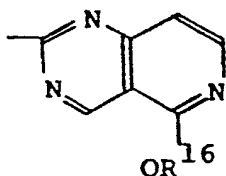




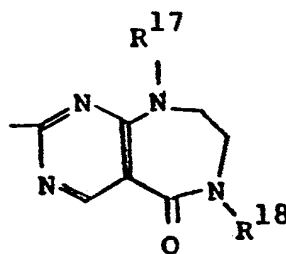
[VIII],



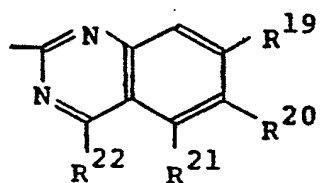
[IX],



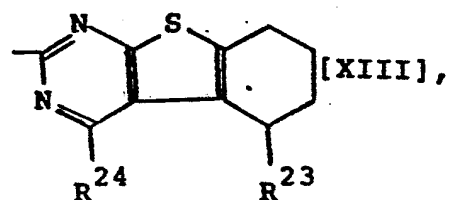
[X],



[XI],



[XII],



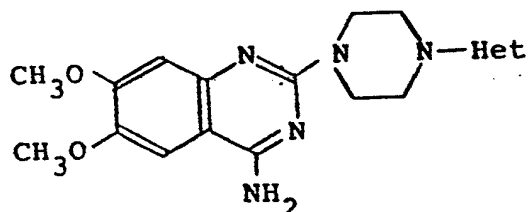
[XIII],

7 wherein,
 8 in the formula [II], either single or double
 9 bond is formed between the 3- and 4-positions, R²
 10 means a hydrogen atom or a lower alkyl, aralkyl, cyano
 11 or formyl group, R³ denotes a hydrogen atom or a
 12 lower alkoxy-carbonyl or phenyl group, R⁴ is a
 13 hydrogen atom or a lower alkyl, lower cycloalkyl,
 14 hydroxy-substituted lower alkyl, lower alkoxy-
 15 substituted lower alkyl, phenyl or aralkyl group, and X
 16 stands for an oxygen or sulfur atom,

17 in the formula [III], either single or double
18 bond is formed between the 2- and 3-positions, and R^5
19 means a hydrogen atom or a lower alkyl group,
20 in the formula [IV], R^6 and R^7 mean
21 individually a hydrogen atom or a lower alkyl group,
22 in the formula [V], R^8 and R^9 mean
23 individually a hydrogen atom or a lower alkyl group,
24 in the formula [VI], m stands for 2 or 3, and
25 R^{10} means a hydrogen atom or a lower alkyl group,
26 in the formula [VII], n stands for an integer of
27 from 2 to 4,
28 in the formula [VIII], R^{11} to R^{13} mean
29 individually a hydrogen atom or a lower alkyl group,
30 in the formula [IX], R^{14} means a hydrogen atom
31 or a hydroxyl, lower alkyl, $-NR^{31}R^{32}$ in which R^{31}
32 is a hydrogen atom or a lower alkyl group and R^{32} is
33 a hydrogen atom or a lower alkyl or lower acyl group,
34 lower alkylthio or lower alkoxy group, R^{15} denotes a
35 lower acyl, lower alkoxycarbonyl, $-CONR^{33}R^{34}$ in
36 which R^{33} is a hydrogen atom or a lower alkyl group,
37 R^{34} is a hydrogen atom or a lower alkyl, phenyl,
38 aralkyl, halogen-substituted lower alkyl or cycloalkyl
39 group or R^{33} and R^{34} couples together to form a
40 methylene moiety which in turn forms a ring having 4 to
41 5 carbon atoms together with the associated nitrogen
42 atom, $-CONHNR^{35}R^{36}$ in which R^{35} and R^{36} are

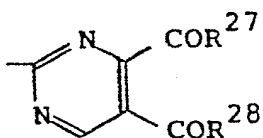
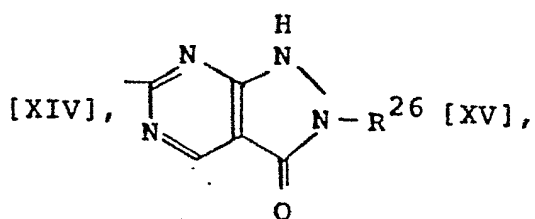
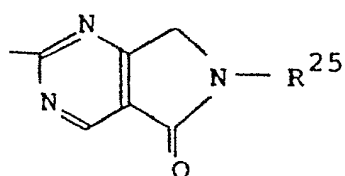
43 individually a lower alkyl group, $-\text{CH}_2\text{CONHR}^{37}$ in
 44 which R^{37} is a lower alkyl, or cyano group,
 45 in the formula [X], R^{16} means a lower alkyl
 46 group,
 47 in the formula [XI], R^{17} and R^{18} mean
 48 individually a hydrogen atom or a lower alkyl group,
 49 in the formula [XII], R^{19} through R^{21} means
 50 a hydrogen atom or a lower alkoxy group, and R^{22}
 51 denotes $-\text{NR}^{38}\text{R}^{39}$ in which R^{38} and R^{39} are
 52 individually a hydrogen atom or a lower alkyl group, or
 53 a hydrogen atom, and
 54 in the formula [XIII], R^{23} means a hydrogen
 55 atom or a lower alkyl group, and R^{24} denotes a
 56 hydrogen atom or a lower alkylthio group.

1 3. A quinazoline derivative represented by the
 2 following general formula [I"] or a pharmacologically
 3 acceptable salt thereof:

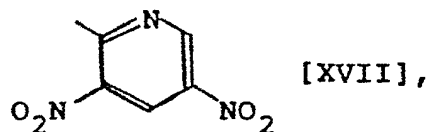


[I"]

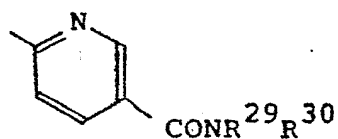
4 wherein Het is represented by any one of the following
 5 formulae [XIV] through [XIX]:



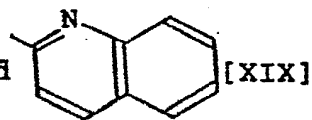
[XVI],



[XVII],



[XVIII], and



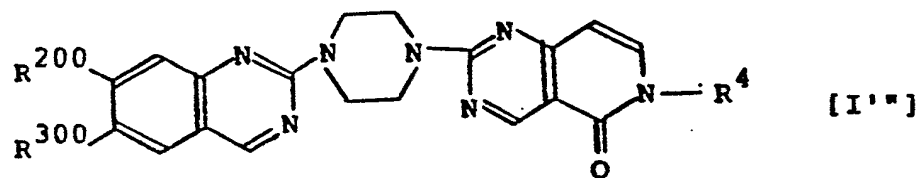
[XIX]

- 6 in the formula [XIV], R^{25} means an alkyl,
 7 cycloalkyl, hydroxy-substituted lower alkyl group,
 8 lower alkoxy-substituted lower alkyl, di(lower
 9 alkylamino)-substituted lower alkyl or aralkyl group,
 10 in the formula [XV], R^{26} means a lower alkyl
 11 group,
 12 in the formula [XVI], R^{27} and R^{28} are either
 13 same or different and mean individually a lower alkoxy,
 14 hydroxyl or lower alkylamino group, or R^{27} and R^{28}
 15 couples together to form a lower alkyl-substituted
 16 imino group, and

- 217 -

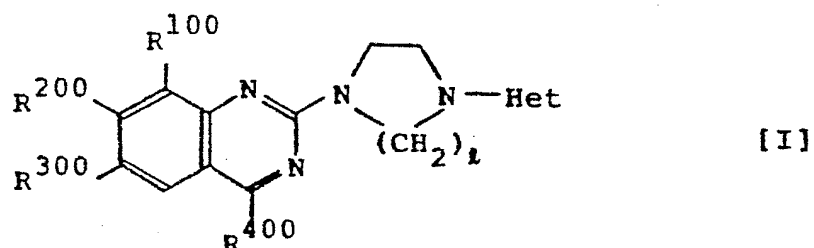
17 in the formula [XVIII], R^{29} and R^{30} are
18 either same or different and mean individually a lower
19 alkyl group.

1 4. A quinazoline derivative represented by the
2 following general formula [I'] or a pharmacologically
3 acceptable salt thereof:

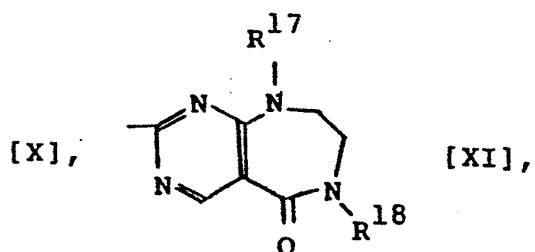
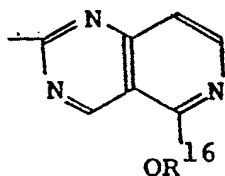
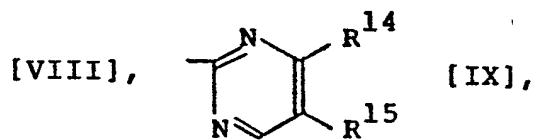
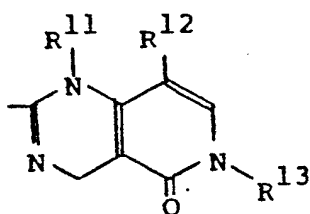
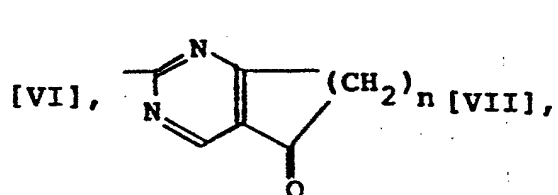
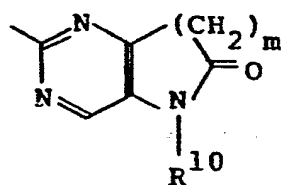
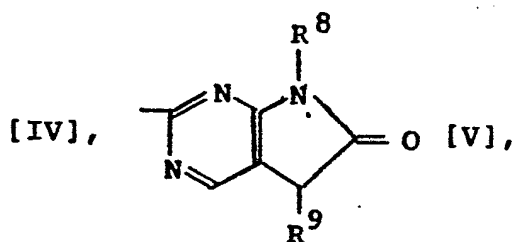
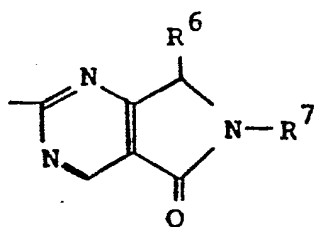
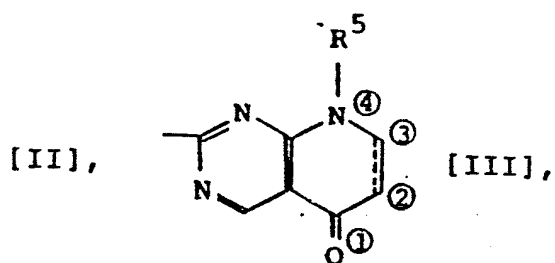
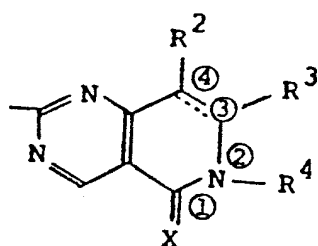


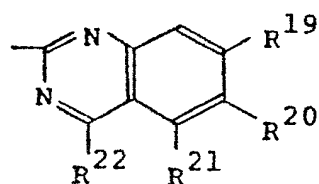
4 wherein R^{200} and R^{300} mean individually a hydrogen
5 atom or lower alkoxy group, and R^4 denotes a lower
6 alkyl group.

1 5. A process for preparing a quinazoline
2 derivative represented by the following general formula
3 [I] or a pharmacologically acceptable salt thereof:

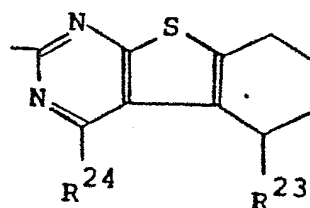


4 wherein R^{100} means a hydrogen atom or methoxy group,
5 R^{200} and R^{300} denote individually a hydrogen atom
6 or lower alkoxy group, R^{400} is a hydrogen atom or
7 amino group, l stands for 2 or 3, and Het is
8 represented by any one of the following formulae [III]
9 through [XIX]:

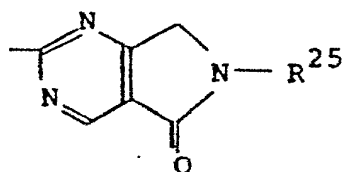




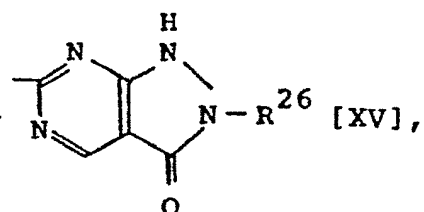
[XII],



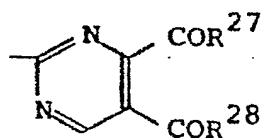
[XIII],



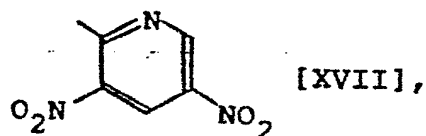
[XIV],



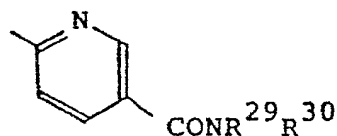
[XV],



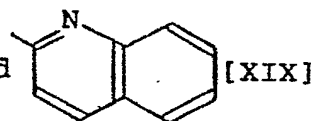
[XVI],



[XVII],



[XVIII], and



[XIX]

10 wherein,
 11 in the formula [III], either single or double
 12 bond is formed between the 3- and 4-positions, R²
 13 means a hydrogen atom or a lower alkyl, aralkyl, cyano
 14 or formyl group, R³ denotes a hydrogen atom or a
 15 lower alkoxy carbonyl or phenyl group, R⁴ is a

16 hydrogen atom or a lower alkyl, lower cycloalkyl,
17 hydroxy-substituted lower alkyl, lower alkoxy-
18 substituted lower alkyl, phenyl or aralkyl group, and X
19 stands for an oxygen or sulfur atom,

20 in the formula [III], either single or double
21 bond is formed between the 2- and 3-positions, and R⁵
22 means a hydrogen atom or a lower alkyl group,

23 in the formula [IV], R⁶ and R⁷ mean
24 individually a hydrogen atom or a lower alkyl group,

25 in the formula [V], R⁸ and R⁹ mean
26 individually a hydrogen atom or a lower alkyl group,

27 in the formula [VI], m stands for 2 or 3, and
28 R¹⁰ means a hydrogen atom or a lower alkyl group,

29 in the formula [VII], n stands for an integer of
30 from 2 to 4,

31 in the formula [VIII], R¹¹ to R¹³ mean

32 individually a hydrogen atom or a lower alkyl group,

33 in the formula [IX], R¹⁴ means a hydrogen atom
34 or a hydroxyl, lower alkyl, -NR³¹R³² in which R³¹

35 is a hydrogen atom or a lower alkyl group and R³² is
36 a hydrogen atom or a lower alkyl or lower acyl group,

37 lower alkylthio or lower alkoxy group, R¹⁵ denotes a
38 lower acyl, lower alkoxycarbonyl, -CONR³³R³⁴ in

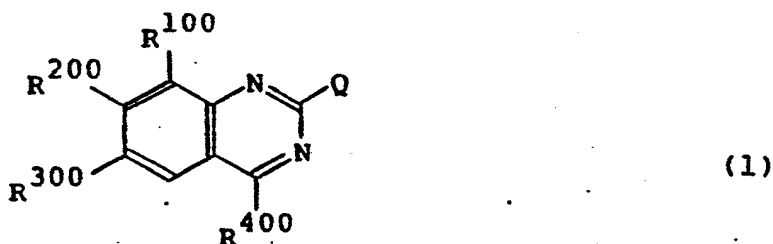
39 which R³³ is a hydrogen atom or a lower alkyl group,

40 R³⁴ is a hydrogen atom or a lower alkyl, phenyl,

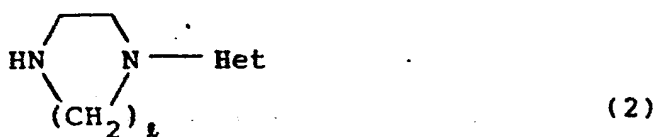
41 aralkyl, halogen-substituted lower alkyl or cycloalkyl

42 group or R^{33} and R^{34} couples together to form a
43 methylene moiety which in turn forms a ring having 4 to
44 5 carbon atoms together with the associated nitrogen
45 atom, $-\text{CONHNR}^{35}\text{R}^{36}$ in which R^{35} and R^{36} are
46 individually a lower alkyl group, $-\text{CH}_2\text{CONHR}^{37}$ in
47 which R^{37} is a lower alkyl, or cyano group,
48 in the formula [X], R^{16} means a lower alkyl
49 group,
50 in the formula [XI], R^{17} and R^{18} mean
51 individually a hydrogen atom or a lower alkyl group,
52 in the formula [XII], R^{19} through R^{21} means
53 a hydrogen atom or a lower alkoxy group, and R^{22}
54 denotes $-\text{NR}^{38}\text{R}^{39}$ in which R^{38} and R^{39} are
55 individually a hydrogen atom or a lower alkyl group, or
56 a hydrogen atom,
57 in the formula [XIII], R^{23} means a hydrogen
58 atom or a lower alkyl group, and R^{24} denotes a
59 hydrogen atom or a lower alkylthio group,
60 in the formula [XIV], R^{25} means an alkyl,
61 cycloalkyl, hydroxy-substituted lower alkyl group,
62 lower alkoxy-substituted lower alkyl, di(lower
63 alkylamino)-substituted lower alkyl or aralkyl group,
64 in the formula [XV], R^{26} means a lower alkyl
65 group,
66 in the formula [XVI], R^{27} and R^{28} are either
67 same or different and mean individually a lower alkoxy,

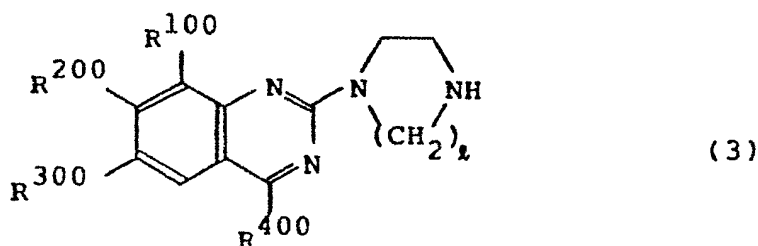
68 hydroxyl or lower alkylamino group, or R^{27} and R^{28}
 69 couples together to form a lower alkyl-substituted
 70 imino group, and
 71 in the formula [XVIII], R^{29} and R^{30} are
 72 either same or different and mean individually a lower
 73 alkyl group, which process comprises: (a) reacting a
 74 compound represented by the following general formula
 75 (1):



76 wherein R^{100} , R^{200} , R^{300} and R^{400} are as
 77 defined above and Q means a readily-removable group,
 78 with a compound represented by the following general
 79 formula (2):



80 wherein l and Het are as defined above, and if the
 81 pharmacologically acceptable salt is desired, further
 82 reacting the reaction product represented by the
 83 general formula [I] with the corresponding nontoxic
 84 acid; or (b) reacting a compound represented by the
 85 following general formula (3):

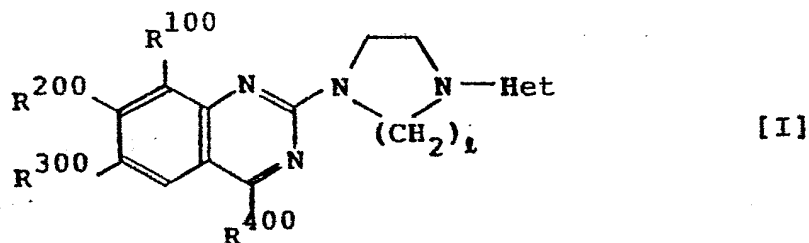


76 wherein R^{100} , R^{200} , R^{300} , R^{400} and l are as
 77 defined above, with a compound represented by the
 78 following general formula (4):



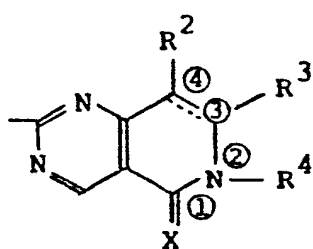
80 wherein Het is as defined above and Q means a readily-
 81 removable group, and if the pharmacologically
 82 acceptable salt is desired, further reacting the
 83 reaction product represented by the general formula [I]
 84 with the corresponding nontoxic acid.

1 5. An antihypertensive preparation comprising,
 2 as an active component, a quinazoline derivative
 3 represented by the following general formula [I] or a
 4 pharmacologically acceptable salt thereof:

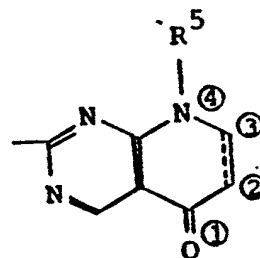


5 wherein R^{100} means a hydrogen atom or methoxy group,
 6 R^{200} and R^{300} denote individually a hydrogen atom
 7 or lower alkoxy group, R^{400} is a hydrogen atom or

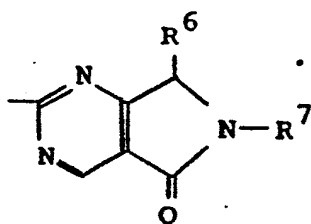
8 amino group, l stands for 2 or 3, and Het is
 9 represented by any one of the following formulae [II]
 10 through [XIX]:



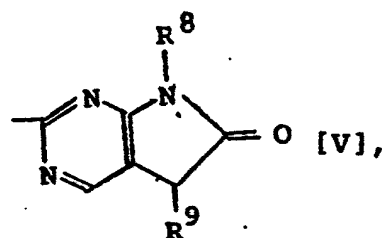
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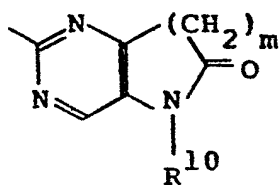
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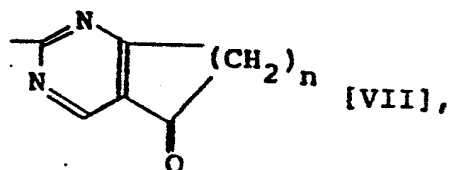
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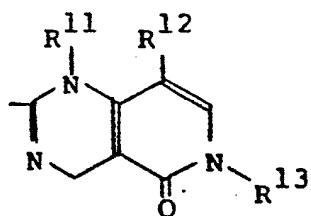
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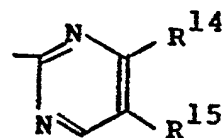
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[VII],

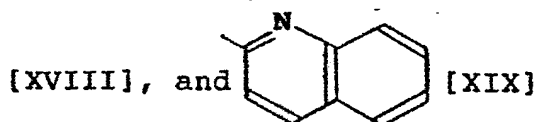
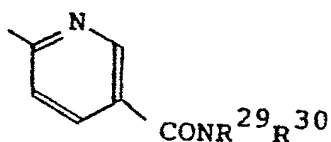
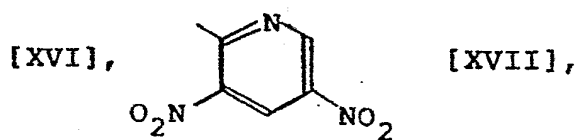
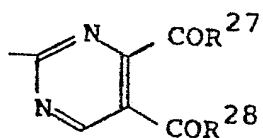
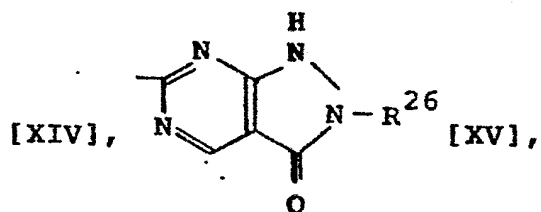
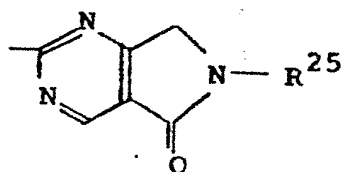
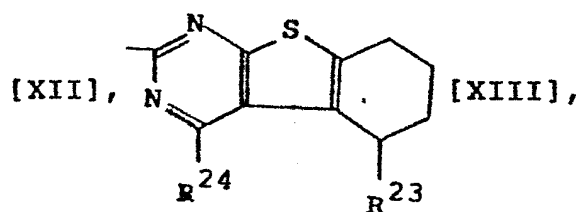
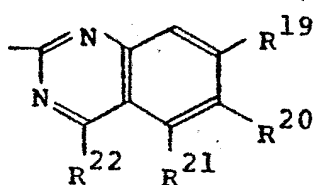
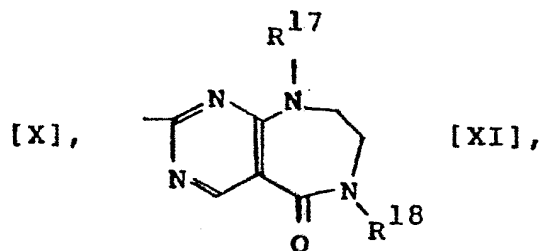
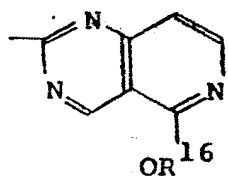


[VIII],



[IX],

- 226 -



11 wherein,

12 in the formula [II], either single or double
13 bond is formed between the 3- and 4-positions, R^2
14 means a hydrogen atom or a lower alkyl, aralkyl, cyano
15 or formyl group, R^3 denotes a hydrogen atom or a
16 lower alkoxy-carbonyl or phenyl group, R^4 is a
17 hydrogen atom or a lower alkyl, lower cycloalkyl,
18 hydroxy-substituted lower alkyl, lower alkoxy-
19 substituted lower alkyl, phenyl or aralkyl group, and X
20 stands for an oxygen or sulfur atom,

21 in the formula [III], either single or double
22 bond is formed between the 2- and 3-positions, and R^5
23 means a hydrogen atom or a lower alkyl group,

24 in the formula [IV], R^6 and R^7 mean
25 individually a hydrogen atom or a lower alkyl group,

26 in the formula [V], R^8 and R^9 mean
27 individually a hydrogen atom or a lower alkyl group,

28 in the formula [VI], m stands for 2 or 3, and
29 R^{10} means a hydrogen atom or a lower alkyl group,

30 in the formula [VII], n stands for an integer of
31 from 2 to 4,

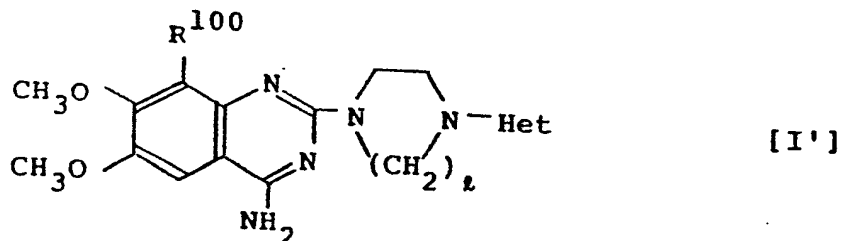
32 in the formula [VIII], R^{11} to R^{13} mean
33 individually a hydrogen atom or a lower alkyl group,

34 in the formula [IX], R^{14} means a hydrogen atom
35 or a hydroxyl, lower alkyl, $-NR^{31}R^{32}$ in which R^{31}
36 is a hydrogen atom or a lower alkyl group and R^{32} is
37 a hydrogen atom or a lower alkyl or lower acyl group,

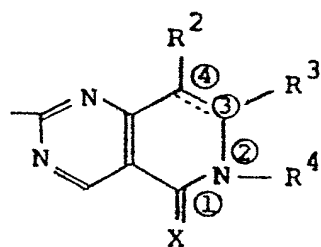
38 lower alkylthio or lower alkoxy group, R^{15} denotes a
39 lower acyl, lower alkoxycarbonyl, $-\text{CONR}^{33}\text{R}^{34}$ in
40 which R^{33} is a hydrogen atom or a lower alkyl group,
41 R^{34} is a hydrogen atom or a lower alkyl, phenyl,
42 aralkyl, halogen-substituted lower alkyl or cycloalkyl
43 group or R^{33} and R^{34} couples together to form a
44 methylene moiety which in turn forms a ring having 4 to
45 5 carbon atoms together with the associated nitrogen
46 atom, $-\text{CONHNR}^{35}\text{R}^{36}$ in which R^{35} and R^{36} are
47 individually a lower alkyl group, $-\text{CH}_2\text{CONHR}^{37}$ in
48 which R^{37} is a lower alkyl, or cyano group,
49 in the formula [X], R^{16} means a lower alkyl
50 group,
51 in the formula [XI], R^{17} and R^{18} mean
52 individually a hydrogen atom or a lower alkyl group,
53 in the formula [XII], R^{19} through R^{21} means
54 a hydrogen atom or a lower alkoxy group, and R^{22}
55 denotes $-\text{NR}^{38}\text{R}^{39}$ in which R^{38} and R^{39} are
56 individually a hydrogen atom or a lower alkyl group, or
57 a hydrogen atom,
58 in the formula [XIII], R^{23} means a hydrogen
59 atom or a lower alkyl group, and R^{24} denotes a
60 hydrogen atom or a lower alkylthio group,
61 in the formula [XIV], R^{25} means an alkyl,
62 cycloalkyl, hydroxy-substituted lower alkyl group,

63 lower alkoxy-substituted lower alkyl, di(lower
 64 alkylamino)-substituted lower alkyl or aralkyl group,
 65 in the formula [XV], R^{26} means a lower alkyl
 66 group,
 67 in the formula [XVI], R^{27} and R^{28} are either
 68 same or different and mean individually a lower alkoxy,
 69 hydroxyl or lower alkylamino group, or R^{27} and R^{28}
 70 couples together to form a lower alkyl-substituted
 71 imino group, and
 72 in the formula [XVIII], R^{29} and R^{30} are
 73 either same or different and mean individually a lower
 74 alkyl group.

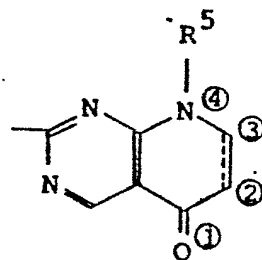
1 7. An antihypertensive preparation comprising,
 2 as an active component, a quinazoline derivative
 3 represented by the following general formula [I'] or a
 4 pharmacologically acceptable salt thereof:



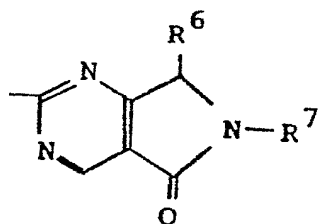
5 wherein R^{100} means a hydrogen atom or a methoxy
 6 group, l stands for 2 or 3, and Het is represented by
 7 any one of the following formulae [II] through [XIII]:



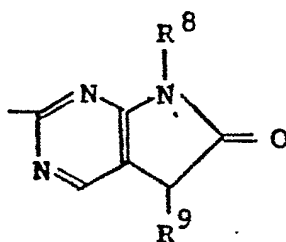
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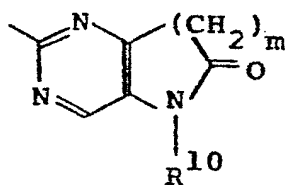
[III],



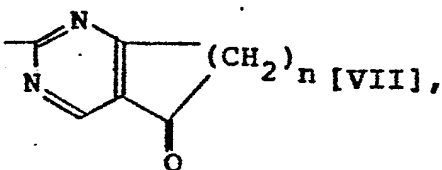
[IV],



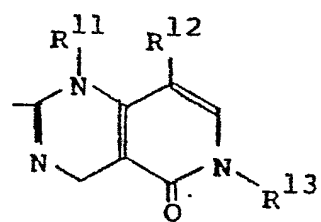
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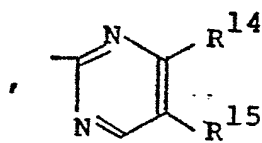
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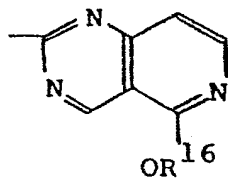
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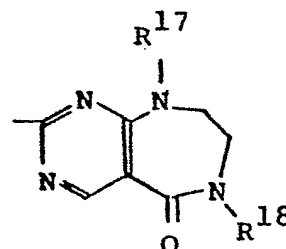
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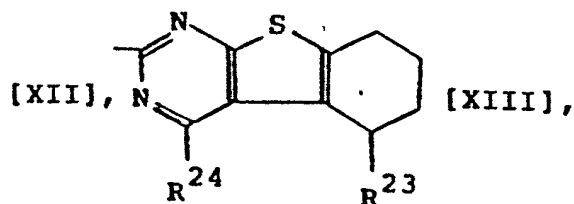
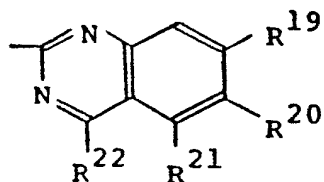
[IX],



[X],



[XI],

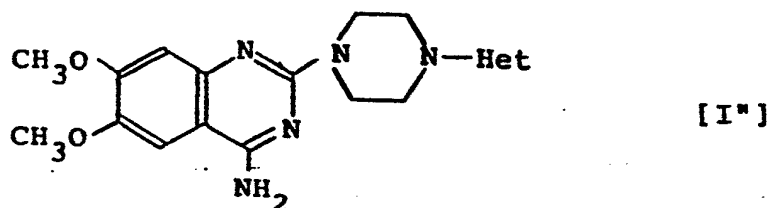


8 wherein,
 9 in the formula [III], either single or double
 10 bond is formed between the 3- and 4-positions, R^2
 11 means a hydrogen atom or a lower alkyl, aralkyl, cyano
 12 or formyl group, R^3 denotes a hydrogen atom or a
 13 lower alkoxy-carbonyl or phenyl group, R^4 is a
 14 hydrogen atom or a lower alkyl, lower cycloalkyl,
 15 hydroxy-substituted lower alkyl, lower alkoxy-
 16 substituted lower alkyl, phenyl or aralkyl group, and X
 17 stands for an oxygen or sulfur atom,
 18 in the formula [III], either single or double
 19 bond is formed between the 2- and 3-positions, and R^5
 20 means a hydrogen atom or a lower alkyl group,
 21 in the formula [IV], R^6 and R^7 mean
 22 individually a hydrogen atom or a lower alkyl group,
 23 in the formula [V], R^8 and R^9 mean
 24 individually a hydrogen atom or a lower alkyl group,
 25 in the formula [VI], m stands for 2 or 3, and
 26 R^{10} means a hydrogen atom or a lower alkyl group,
 27 in the formula [VII], n stands for an integer of
 28 from 2 to 4,

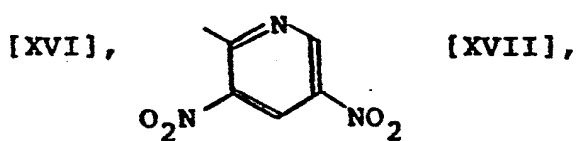
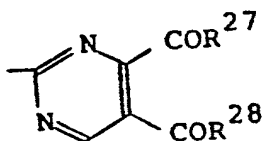
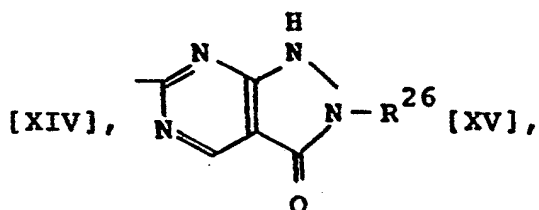
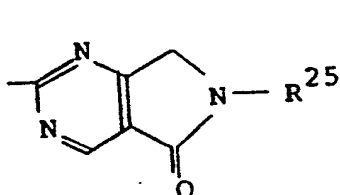
29 in the formula [VIII], R^{11} to R^{13} mean
30 individually a hydrogen atom or a lower alkyl group,
31 in the formula [IX], R^{14} means a hydrogen atom
32 or a hydroxyl, lower alkyl, $-NR^{31}R^{32}$ in which R^{31}
33 is a hydrogen atom or a lower alkyl group and R^{32} is
34 a hydrogen atom or a lower alkyl or lower acyl group,
35 lower alkylthio or lower alkoxy group, R^{15} denotes a
36 lower acyl, lower alkoxycarbonyl, $-CONR^{33}R^{34}$ in
37 which R^{33} is a hydrogen atom or a lower alkyl group,
38 R^{34} is a hydrogen atom or a lower alkyl, phenyl,
39 aralkyl, halogen-substituted lower alkyl or cycloalkyl
40 group or R^{33} and R^{34} couples together to form a
41 methylene moiety which in turn forms a ring having 4 to
42 5 carbon atoms together with the associated nitrogen
43 atom, $-CONHNR^{35}R^{36}$ in which R^{35} and R^{36} are
44 individually a lower alkyl group, $-CH_2CONHR^{37}$ in
45 which R^{37} is a lower alkyl, or cyano group,
46 in the formula [X], R^{16} means a lower alkyl
47 group,
48 in the formula [XI], R^{17} and R^{18} mean
49 individually a hydrogen atom or a lower alkyl group,
50 in the formula [XII], R^{19} through R^{21} means
51 a hydrogen atom or a lower alkoxy group, and R^{22}
52 denotes $-NR^{38}R^{39}$ in which R^{38} and R^{39} are
53 individually a hydrogen atom or a lower alkyl group, or
54 a hydrogen atom, and

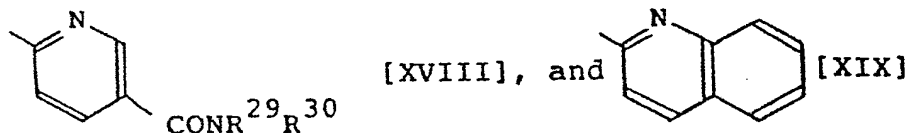
55 in the formula [XIII], R^{23} means a hydrogen
 56 atom or a lower alkyl group, and R^{24} denotes a
 57 hydrogen atom or a lower alkylthio group.

1 8. An antihypertensive preparation comprising,
 2 as an active component, a quinazoline derivative
 3 represented by the following general formula [I*] or a
 4 pharmacologically acceptable salt thereof:



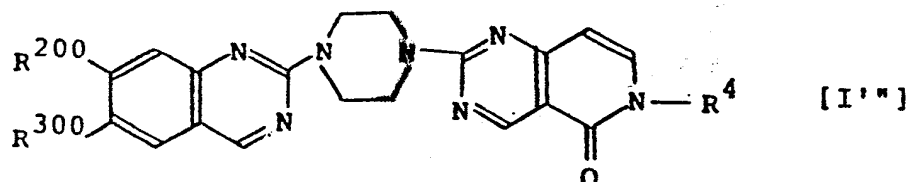
5 wherein Het is represented by any one of the following
 6 formulae [XIV] through [XIX]:





7 in the formula [XIV], R^{25} means an alkyl,
 8 cycloalkyl, hydroxy-substituted lower alkyl group,
 9 lower alkoxy-substituted lower alkyl, di(lower
 10 alkylamino)-substituted lower alkyl or aralkyl group,
 11 in the formula [XV], R^{26} means a lower alkyl
 12 group,
 13 in the formula [XVI], R^{27} and R^{28} are either
 14 same or different and mean individually a lower alkoxy,
 15 hydroxyl or lower alkylamino group, or R^{27} and R^{28}
 16 couples together to form a lower alkyl-substituted
 17 imino group, and
 18 in the formula [XVIII], R^{29} and R^{30} are
 19 either same or different and mean individually a lower
 20 alkyl group.

1 9. An antihypertensive preparation comprising,
 2 as an active component, a quinazoline derivative
 3 represented by the following general formula [I'] or a
 4 pharmacologically acceptable salt thereof:



5 wherein R²⁰⁰ and R³⁰⁰ mean individually a hydrogen
 6 atom or lower alkoxy group, and R⁴ denotes a lower
 7 alkyl group.

1 10. An antihypertensive preparation according to
 2 any one of claims 6 to 9 also comprising a pharmaceuti-
 3 cally acceptable carrier.

1 11. An antihypertensive preparation according to
 2 any one of claims 6 to 10 also comprising one or more
 3 other active antihypertensive components and/or
 4 diuretics.

1 12. The compound as claimed in any one of claims
 2 1 to 4 for use in the treatment of hypertension or heart
 3 failure.

1 13. Use of the compound as claimed in any one
 2 of claims 1 to 4 for the manufacture of a medicament
 3 for treating hypertension or heart failure.

DERWENT-ACC-NO: 1986-190941

DERWENT-WEEK: 199319

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TITLE: New 2-N'-heterocyclyl-piperazinyl-quinazoline(s) and analogues useful as potent and prolonged action antihypertensives without undesirable side effects

INVENTOR: AWAYA A; KATO K ; KATOU K ; KATOU S ; KITAHARA T ; KUMAKURA M ; NAKANO T ; NISHINA T ; OHNO H ; ONO H ; SARUTA S ; WATANABE K ; YOKOYAMA K

PATENT-ASSIGNEE: MITSUI PETROCHEM IN[MITC] , MITSUI PETROCHEM IND CO LTD [MITC] , MITSUI PHARM INC [MITH] , MITSUI PHARMACEUTICAL CO [MITH]

PRIORITY-DATA: 1985JP-204463 (September 18, 1985) , 1984JP-263015 (December 14, 1984) , 1985JP-194968 (September 5, 1985)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE
EP 188094 A	July 23, 1986	EN
JP 61140568 A	June 27, 1986	JA
JP 62056488 A	March 12, 1987	JA
JP 62067077 A	March 26, 1987	JA
HU 42479 T	July 28, 1987	HU
US 4734418 A	March 29, 1988	EN
JP 91071430 B	November 13, 1991	JA
EP 188094 B	March 18, 1992	EN
DE 3585680 G	April 23, 1992	DE
CA 1307786 C	September 22, 1992	EN
JP 93028709 B	April 27, 1993	JA

DESIGNATED-STATES: DE FR GB IT DE FR GB IT

APPLICATION-DATA:

PUB-NO	APPL- DESCRIPTOR	APPL-NO	APPL-DATE
EP 188094A	N/A	1985EP- 309049	December 12, 1985
JP 61140568A	N/A	1984JP- 263015	December 14, 1984
JP 93028709B	N/A	1984JP- 263015	December 14, 1984
JP 62056488A	N/A	1985JP- 194968	September 5, 1985
JP 91071430B	N/A	1985JP- 194968	September 5, 1985
JP 62067077A	N/A	1985JP- 204463	September 18, 1985

CA 1307786C	N/A	1985CA-497106	December 6, 1985
US 4734418A	N/A	1985US-805905	December 6, 1985
EP 188094B	Based on	1985EP-309049	December 12, 1985

INT-CL-CURRENT:

TYPE	IPC DATE
CIPP	C07D211/86 20060101
CIPP	C07D401/12 20060101
CIPP	C07D471/04 20060101
CIPS	A61K31/505 20060101
CIPS	A61K31/517 20060101
CIPS	A61K31/55 20060101
CIPS	A61P9/12 20060101
CIPS	C07D213/00 20060101
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CIPS	C07D495/04	20060101
CIPS	C07D495/04	20060101

ABSTRACTED-PUB-NO: EP 188094 A

BASIC-ABSTRACT:

2-N'-Heterocyclyl piperazinyquinazolines and analogues of formula (I) and their salts are new, where R'¹ = H or MeO; R'², R'³ = H or lower alkoxy; R'⁴ = H or NH₂; l = 2 or 3; Het = gp. of formulae e.g. (111a)-(111m); in (IIIa) and (IIIb) the broken bonds are opt. double bonds; R₂ = H, lower alkyl, aralkyl, CN or HCO; R₃ = H, lower alkoxycarbonyl or Ph; R₄ = H, lower alkyl, lower cycloalkyl, lower hydroxyalkyl, lower alkoxy-lower alkyl, Ph or aralkyl; X = O or S; R₅-R₁₃ = H or lower alkyl; m = 2 or 3; n = 2, 3 or 4; R₁₄ = H, OH, lower alkyl, NR₃₁R₃₂, lower alkylthio or lower alkoxy; R₁₅ = lower acyl, lower alkoxycarbonyl, CONR₃₃R₃₄, CONHNR₃₅R₃₆, CH₂CONHR₃₇ or CN; R₃₁, R₃₃ = H or lower alkyl; R₃₂ = H, lower alkyl or lower acyl; R₃₄ = H, lower alkyl, Ph, aralkyl, lower haloalkyl or cycloalkyl; or R₃₃+R₃₄ = (CH₂)₄ or (CH₂)₅; R₁₆, R₃₅-R₃₇ = lower alkyl; R₁₇, R₁₈ = H or lower alkyl; R₁₉-R₂₁ = H or lower alkoxy; R₂₂ = H or NR₃₈R₃₉; R₂₃, R₃₈, R₃₉ = H or lower alkyl; R₂₄ = H or lower alkylthio; R₂₅ = alkyl, cycloalkyl, lower hydroxyalkyl, lower alkoxy-lower alkyl, di-(lower alkylamino)-lower alkyl or aralkyl .

USE/ADVANTAGE - (I) are potent and prolonged action antihypertensives, but orthostatic hypotension is not observed as a side effect. Dose

is 0.0001-200 mg/kg daily.

TITLE-TERMS: NEW HETEROCYCLE PIPERAZINYL
QUINAZOLINE ANALOGUE USEFUL POTENCY
PROLONG ACTION ANTIHYPERTENSIVE
UNDESIRABLE SIDE EFFECT

DERWENT-CLASS: B02

CPI-CODES: B06-D06; B12-F05;

CHEMICAL-CODES: Chemical Indexing M2 *01*
Fragmentation Code D011 D012 D013
D014 D015 D019 D021 D022 D023
D024 D029 D621 D740 D790 D840
D850 D860 D920 D970 E850 F011
F012 F013 F014 F015 F019 F423
F431 F433 F541 F542 F553 F560
G010 G019 G030 G039 G040 G050
G100 G111 G112 G113 G530 G543
G553 G563 G573 G599 H1 H100 H101
H102 H103 H122 H123 H181 H2 H202
H203 H211 H322 H401 H481 H521
H541 H542 H543 H581 H592 H600
H601 H602 H608 H609 H681 H682
H683 H684 H685 H686 H689 J011
J012 J111 J112 J211 J212 J311
J312 J321 J371 J411 J521 J522
J561 J581 J592 K620 L142 L640
L910 L922 L930 L941 L943 L999
M113 M121 M123 M129 M132 M135
M136 M139 M150 M210 M211 M212
M213 M214 M215 M216 M220 M221
M222 M231 M232 M233 M240 M262
M271 M272 M273 M280 M281 M282
M283 M311 M312 M313 M314 M315
M320 M321 M322 M331 M332 M333
M334 M340 M342 M343 M344 M362

M372 M373 M383 M391 M412 M511
M512 M521 M522 M530 M531 M532
M533 M540 M541 M630 M640 M650
M710 P526 Ring Index Numbers
00347 01174 01261 01363 01602
01603 01605 08124 10066 11882
40103 61769

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